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Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Impact of Community Pharmacists on Management of Cancer Chemotherapy and the Resulting Side Effects

Jacquline M. Nunner, fourth-year pharmacy student from Dayton, Ohio; Jessica Stemen, fourth-year pharmacy student from Gahanna, Ohio; Courtney Porter, fifth-year pharmacy student from Canfield, Ohio; Ellen Hazelet, fifth-year pharmacy student from Columbia City, Ind.; Mark Olah, R.Ph., Ph.D., associate professor of pharmacology

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-12-032-H01-P

Objectives

1. Identify the most common chemotherapy-induced side effects and associated signs and symptoms.
2. Identify commonly dispensed oral chemotherapy agents associated with chemotherapy-induced side effects.
3. State possible pharmacologic treatments for the most common chemotherapy-induced side effects.
4. Recognize non-pharmacologic ways in which community pharmacists can help manage chemotherapy-induced side effects.
5. Identify resources available to community pharmacists to help manage chemotherapy-induced side effects.
6. Recognize common limitations prohibiting community pharmacists from being able to manage chemotherapy -induced side effects.

Abstract

The severe side effects of chemotherapy negatively affect quality of life and may limit the amount of life-saving drug delivered to patients with cancer. These adverse events can be difficult to manage and evidence-based guidelines are lacking. Insufficient supportive care can amplify common side effects, such as chemotherapy-induced nausea and vomiting (CINV), myelosuppression, alopecia, gastrointestinal effects and neuropathy. Therefore, it is important to recognize the most commonly dispensed chemotherapy agents and the side effects that accompany them. Community pharmacists, as easily accessible health care professionals, can provide valuable supportive care to help manage potentially debilitating side effects. However, a major limitation when managing side effects secondary to chemotherapy is the limited access to patient information in most community pharmacies. By allowing community pharmacists increased access to patient health records using technology, limitations experienced in practice can be averted and quality care provided.

Introduction

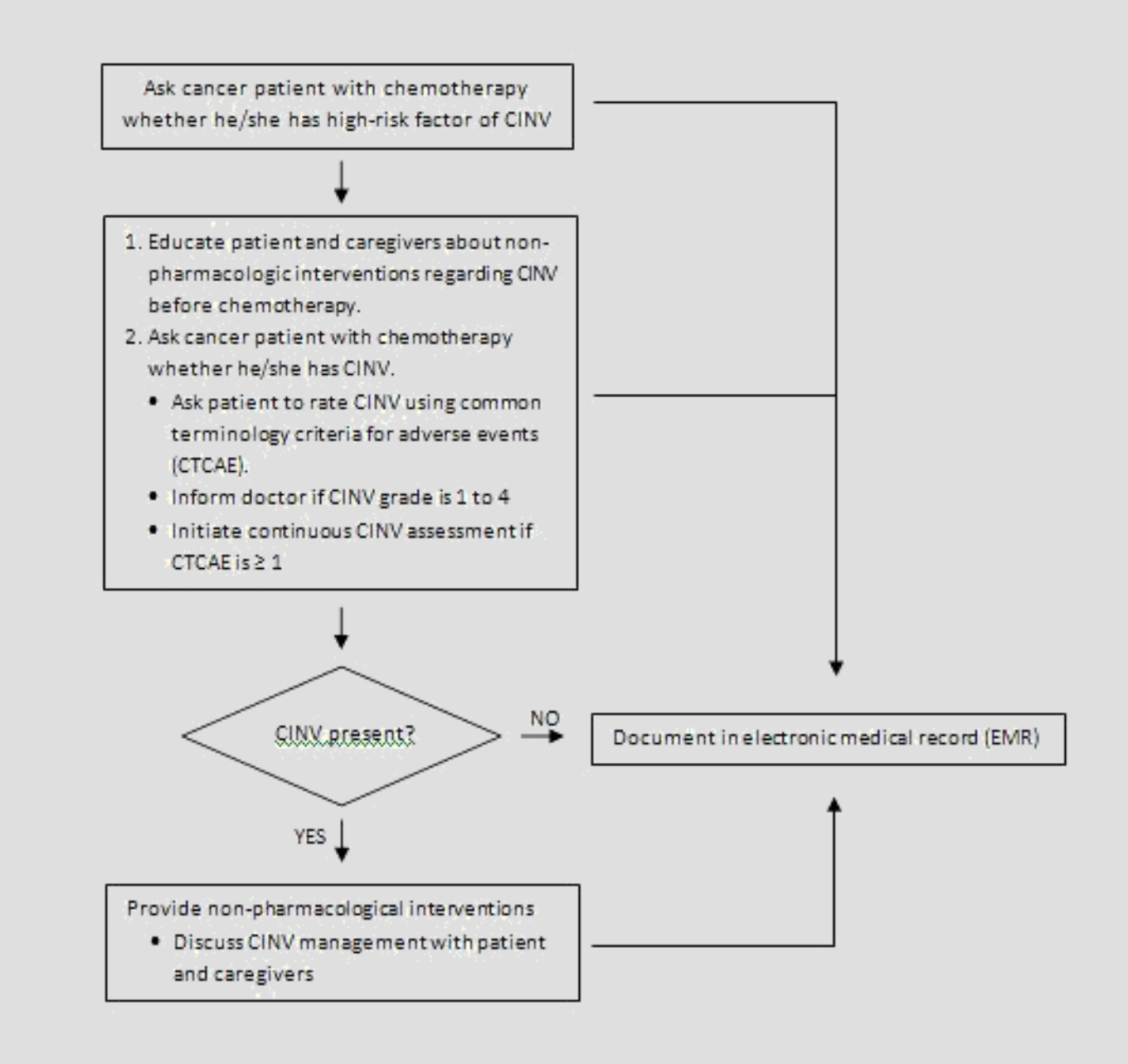
Hardships endured by cancer patients are often worsened by the severe side effects of chemotherapy. As health care professionals who are easily accessible to patients, community pharmacists can provide valuable supportive care to help manage potentially debilitating side effects in individuals undergoing chemotherapy. This is especially true when dispensing oral agents that do not require administration within an outpatient clinic. While the chemotherapy regimens are often determined by strict evidence-based guidelines, the supportive care offered to patients is not as well-controlled.[1] Insufficient supportive care can amplify the side effects of chemotherapy endured by patients such as chemotherapy-induced nausea and vomiting (CINV), myelosuppression, alopecia, gastrointestinal effects and neuropathy. A major obstacle to pharmacist involvement in managing side effects secondary to chemotherapy is the lack of access to patient information in most community pharmacies. By increasing pharmacists' access to patient health records using technology, limitations experienced in practice can be minimized to improve the community pharmacist's ability to provide quality care.

Most Common Oral Chemotherapy Side Effects

Debilitating as the disease itself may be, the difficulties faced by patients with cancer are often compounded by the harsh side effects of CINV, diarrhea, constipation, neutropenia, anemia and neuropathy. Despite advances in antiemetic agents, CINV deters many cancer patients from completing otherwise beneficial treatment regimens, and thus remains a paramount concern when antineoplastic treatment is initiated. In addition to causing withdrawal from treatment, nausea and vomiting can have detrimental effects such as serious metabolic disorders, nutritional depletion and anorexia, deterioration of patients' physical and mental status, esophageal tears, fractures and wound dehiscence.[2] CINV has variable onset, ranging from anticipatory (prior to chemotherapy administration), acute (within 24 hours of initial chemotherapy administration) or delayed (occurring 24 hours to days following treatment).[3] Methotrexate (Rhematrex®), temozolomide (Temodar®) and capecitabine (Xeloda®) are commonly dispensed oral chemotherapy agents associated with CINV. Figure 1 outlines an algorithm for the treatment of CINV in an acute care setting. Options for the non-pharmacological management of CINV, as seen in Table 1, include wearing loose-fitting clothing and eating small, frequent meals. Patients may consider eating toast, crackers, and yogurt; eating ice cubes before meals may also reduce symptoms of CINV. Patients should also drink water throughout chemotherapy to prevent dehydration. Simple hygiene in keeping the oral cavity clean can also help in the management of CINV. Eating before a session of chemotherapy and lying flat after meals are not recommended.

Antiemetic agents are commonly prescribed to help treat CINV pharmacologically.[4] Table 2 lists several chemotherapy agents at various risk categories for CINV and further offers

Figure 1. Flowchart of CINV Management.[19]



an antiemetic schedule for consideration. Current CINV recommendations include a combination of a neurokinin 1 (NK_1) receptor antagonist, a 5-HT_3 receptor antagonist and dexamethasone, depending on the emetic risk (mild, moderate or severe) of the chemotherapeutic agent.[5] However, breakthrough CINV can occur and it is necessary for clinicians to monitor a patient's response to antiemetic agents throughout chemotherapy to maintain optimal treatment. Non-pharmacologic treatments such as dietary alterations or acupuncture have also been explored.

Diarrhea is consistently poorly monitored and underreported despite being one of the most prevalent side effects of chemotherapeutic agents, especially those regimens containing Adrucil® (5-fluorouracil or 5-FU) and irinotecan (Camptosar®). Complications can range from suboptimal

Table 1: Non-pharmacological Management of CINV[19]

- Wear loose fitting clothing
- Eat small, frequent meals
- Avoid sweet, fatty, high-salt, or spicy foods
- Eat toast, crackers, and yogurt; drink lemon, grapefruit, and ginger teas
- Eat ice cubes before meals and chemotherapy sessions
- Do not lie flat after meals
- Keep the oral cavity clean
- Take deep breaths through the mouth, and place cold towels on head and neck
- Discuss uncontrolled symptoms with health care professionals

therapy to fatality. Prior to treatment, clinicians may evaluate risk factors for diarrhea, including age, gender, bowel pathology, and chemotherapy schedule. Should the patient experience chemotherapy-induced diarrhea, assessment of possible contributing factors such as diet, infection, disease states implicated in malabsorption or inflammation and confounding medications is necessary. Because of the variation in onset, it is recommended that patients at risk or who have developed treatment-induced diarrhea are monitored throughout therapy. Intervention consists of both pharmacologic and non-pharmacologic measures, depending on the severity and duration of the diarrhea. Some oral agents known to cause diarrhea include lapatinib (Tykerb®), erlotinib (Tarceva®) and sorafenib (Nexavar®).[6,7,8] The National Cancer Institute (NCI) classifies the stages of diarrhea as shown in Table 3.[6] Table 4 offers appropriate options for the management of each of these stages according to the American Society of Clinical Oncology (ASCO). First-line treatment of uncomplicated diarrhea consists of loperamide at a standard dose (initially 4 mg, then 2 mg every four hours or after every unformed stool; maximum of 16 mg per day) or an increased dose for persistent symptoms if physician recommended. The drug octreotide is indicated in loperamide refractory diarrhea and as a preliminary treatment in complicated diarrhea. Fluoroquinolone antibiotics or vancomycin are recommended for prophylaxis or if infectious diarrhea is suspected. Other treatments such as atropine, budesonide, diphenoxylate, activated charcoal or probiotics are less commonly used.[9]

Like diarrhea, constipation is also a common side effect of numerous chemotherapy treatments that is underreported and undertreated. Patients undergoing chemotherapy may suffer from constipation due to a number of reasons including dehydration, neuropathy, decreased exercise tolerance, electrolyte imbalances, antiemetic agents and use of analge-

Table 2: Emesis Risk of Various Chemotherapy Agents and Proposed CINV Treatment[4]

Emetic Risk	Chemotherapeutic drug	Antiemetic schedule
High (>90%)	Cisplatin, Mechlorethamine, Streptozocin, Dacarbazine, Carmustine, Dactinomycin, Cyclophosphamide (>1500 mg/m^2)	5-HT$_3$ serotonin receptor antagonist: Day 1 Dexamethasone: Days 1-4 Aprepitant: Days 1-3
Moderate (30 to 90%)	Oxaliplatin, Cytarabine (>1000 mg/m^2), Carboplatin, Ifosfamide, Cyclophosphamide (<1500 mg/m^2), Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Idarubicin, Irinotecan	5-HT3 serotonin receptor antagonist: Day 1 Dexamethasone: Day 1(2,3)[a] (Aprepitant: Days 1,2,3)
Low (10 to 30%)	Paclitaxel, Docetaxel, Mitoxantrone, Topotecan, Etoposide, Pemetrexed, Methotrexate, Mitomycin, Gemcitabine, Cytarabine (<1000 mg/m^2), Fluorouracil, Bortezomib, Cetuximab, Trastuzumab	Dexamethasone: Day 1
Minimal (<10%)	Bevacizumab, Bleomycin, Busulfan, Fludarabine, Vincristine, Vinorelbine, Vinblastine, 2-Chlorodeoxyadenosine, Rituximab	Prescribe as needed

[a]May omit days 2 and 3 if aprepitant is given; for patients receiving a combination of anthracycline and cyclophosphamide

Table 3: NCI Classification of Stages of Diarrhea

Toxicity Grade	Diarrhea
1	Increase of <4 stools/day over baseline Mild increase in ostomy output compared with baseline
2	Increase of 4-6 stools/day over baseline Intravenous fluids >24 hours Moderate increase in ostomy output compared with baseline Not interfering with daily living
3	Increase of >7 stools/day over baseline Incontinence Intravenous fluids Severe increase in ostomy output compared with baseline Interfering with daily living activities
4	Life-threatening consequences (e.g., hemodynamic collapse)
5	Death

Table 4: ASCO Recommended Guidelines for the Management of Treatment-induced Diarrhea[6]

Diarrhea CTC grade	Management
Uncomplicated grade 1-2	Stop all lactose containing products Drink 8 to 10 large glasses of liquid/day Eat frequent small meals
Grade 2	Hold cytotoxic chemotherapy and consider lapatinib dose reduction Administer standard dose of loperamide (consider continuation of loperamide until diarrhea-free for 12 hours)
Grade 3 or 4 diarrhea or grade 1 or 2 with complicating features[a]	Consider hospital admission Administer octreotide Use intravenous fluids if appropriate Use prophylactic antibiotics as needed (especially if diarrhea is persistent beyond 24 hours or there is fever or grade 3-4 neutropenia) Hold both cytotoxic chemotherapy and lapatinib

[a]Grade 3 cramping, nausea/vomiting, decreased performance status from baseline; >grade 2 fever, any sepsis, grade 3 or 4 neutropenia, grade 3 bleeding, grade 2 dehydration.

sics. Those chemotherapeutic agents that cause constipation most commonly are the vinca alkaloids, platinums and hormonal agents.[10] Table 5 indicates treatment guidelines for prophylaxis and care of those patients suffering from chemotherapy-induced constipation.

Neutropenia is a significant side effect because toxicity related to neutropenia limits the dose of chemotherapy that can be tolerated. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 cells/mm^3 or an ANC that is expected to decrease to less than 500 cells/mm^3 during the next 48 hours of monitoring.[11] The degree and duration of neutropenia predispose the chemotherapy patient to infection due to suppression of the production of neutronphils, a key component of innate immunity and a significant sign of infection.[12] Although all chemotherapy patients are at risk of developing neutropenia, challenges still exist in determining those populations at a greater risk, and presentation of chemotherapy-induced neutropenia may be limited to a fever alone. Prevention of infection is key, and antibiotic, antiviral or antifungal prophylactic therapy is based on patient characteristics.[11] It is important for pharmacists to stress the increased risk of infection to patients and educate them on the signs and symptoms. While it is difficult to recommend pharmacologic treatment from a community pharmacist's setting, non-pharmacologic suggestions can be made, including limiting exposure to infection by practicing good hygiene and avoiding crowded public areas.

Anemia may originate from decreased production of red blood cells (RBCs), increased destruction of RBCs or blood loss, and is characterized by a decrease in normal hemoglobin concentration or RBC count. In patients undergoing cancer treatment, this may result from the myelosuppressive nature of cytotoxic chemotherapy such as Sutent® (sunitinib), or from the disease itself. Patients suffering from anemia can experience dizziness, fatigue and shortness of breath. In addition to significantly altering quality of life, anemia may further complicate treatment due to delays associated with therapy. Typically anemia is treated using erythropoiesis-stimulating agents (ESAs), blood transfusions or iron supplementation to maintain hemoglobin levels and patients should be directed to their physician for treatment.[13] Educating patients on the signs and symptoms of anemia and quickly re-

Table 5: NCCN Constipation Treatment Guidelines[20]

	Non-pharmacologic	Pharmacologic
Prophylactic	Increase fluids Increase dietary fiber Exercise if appropriate	Stimulant laxative + stool softener
Constipation	Rule out impaction/obstruction Treat other causes (hypercalcemia, hypokalemia, hypothyroidism, DM, medications)	Add and titrate bisacodyl 10-15 mg TID with goal of 1 non-forced BM Q 1-2 days
Persistent Constipation	Reassess for cause/severity Recheck for impaction/obstruction	Consider adding other laxatives such as polyethylene glycol, sorbitol, magnesium hydroxide, magnesium citrate, enema, prokinetic agent (metoclopramide)

ferring them back to their physician is the best non-pharmacologic way to care for this side effect from a community pharmacist's standpoint.

Neuropathy presents as a difficult side effect of many chemotherapeutic agents, both in terms of diagnosis and treatment. Unlike anemia, which can be diagnosed based on lab values and symptoms, neurologists managing cancer patients must rely largely on the pattern of neuropathy associated with specific agents. Neurotoxicity is often dependent on the cumulative dose of the treatment; severity of neuropathy increases with the duration of treatment and progression is halted with termination of treatment. Loss of sensations, paresthesia, pain and loss of motor function all vary depending on schedule of treatment and the agent used. Common chemotherapeutic agents implicated in neuropathy include platinum compounds, vinca alkaloids and taxanes. Because treatment of chemotherapy-induced neuropathy is typically symptomatic, prevention and management of risk factors, such as pre-existing neuropathy upon initiation of treatment, is key in this patient population.[14]

Oncology Resources

When patients inquire about other side effects not addressed above, there are a few educational resources for further information. These include The NCCN Clinical Practice Guidelines in Oncology website (http://www.nccn.org) which separates treatment guidelines by site and often includes a section on supportive care specific to each cancer type. Additionally, access to relevant literature and case reports in oncology can be found at the American Society of Clinical Oncology website (http://www.asco.org). Lastly, but perhaps most importantly, contacting a board certified clinical oncology pharmacist who deals with these drugs on a daily basis would most likely provide the information necessary to inform the patient. When used together, these resources can help community pharmacists not entirely familiar with chemotherapeutic drugs provide excellent, continuous care to patients undergoing chemotherapy.

Clinical Trials

Chauvelot et al. 2010[15]

Community pharmacists currently aid in the management of multiple chronic disease states such as heart failure. Many of the principle strategies and services employed in heart failure care are applicable to the management of cancer chemotherapy as well. Chauvelot and colleagues used two sets of surveys to determine the role of the pharmacist in heart failure management from the viewpoints of both patients and pharmacists.[15] Patients viewed community pharmacists as a medication therapy specialist, but less than 40 percent of survey participants felt the pharmacist should take on larger roles in therapy management such as disease explanation and medical follow-up. Pharmacists felt they were knowledgeable about the disease state and could educate the heart failure patient in 68 percent of cases. Community pharmacists are ideally placed to educate patients about their disease states and improve medication adherence, in addition to traditional roles as drug dispensing experts. The difficulty arises in overcoming current perceptions about the role of the community pharmacist from both patients and other health care providers. Pharmacists must also be empowered to play a larger role in disease state management through continuing education.

Dohler et al. 2011[16]

The objective of a study by Dohler et al. was to identify responsibilities of health care professionals in the management of cancer chemotherapy by using focus group discussions consisting of clinical pharmacists with a background in cancer care.[16] Clinical pharmacists, physicians and nurses used a two-round Delphi process to allocate the identified responsibilities specifically to the aforementioned professionals. Members of the DKG, Germany's largest multiprofessional association in oncology, completed a survey to rate their acceptance of the proposed tasks and their allocation to various professions. The study identified areas for pharmacist involvement in patient education and counseling in addition to the prevention of drug related problems. Results showed that the pharmacist's role included eight of 11 proposed patient education tasks focused on increasing medication compliance. Pharmacists were also pertinent to seven of 20 proposed tasks in preventing medication issues, including screening for interactions. With up to 75 percent of cancer patients using oral, complementary chemotherapy treatments, the role of the pharmacist is crucial. Unfortunately, according to additional surveys, pharmacists are not yet able to perform their allocated tasks. The primary issue is that pharmacists do not feel as though they are an integral part of the health care team. However, as evidenced by the allocation of tasks, physicians, nurses and pharmacists are all necessary to effectively manage a patient's cancer chemotherapy regimen.

Community pharmacists can practice some of the roles proposed for clinical pharmacists in this study. Patient education, improving medication adherence and screening for drug -drug interactions are all tasks that are performed on a regular basis in the community pharmacy. Pharmacists currently use these services to manage heart failure; the same strategy can be applied to cancer chemotherapy.

Simons et al. 2011[17]

Additionally, in a study assessing intensified pharmaceutical care, Simons et al. conducted a prospective, multi-centered, observational cohort study with control group.[17] The intervention group in the study received intensified pharmaceutical care. Subjects were recruited from three hospitals. Fifty subjects were enrolled in the study and divided evenly between the control group and intervention group. The intensified pharmaceutical care included education about the drug capecitabine, details on the treatment regimen, risks of non-compliance and information on other current medications all from a registered pharmacist. Later, subjects received a medication dosing schedule and information on possible adverse events including preventative methods. A pharmacist contacted each subject in the intervention group once during each cycle of chemotherapy via telephone to answer questions and provide further counseling.

Adherence to medication therapy was monitored using a Micro Electronic Monitoring (MEMS™) vial that registered every time the subject opened the container. Limitations of the MEMS™ system include the inability to determine if the patient actually swallowed the medication and how many pills the patient took out of the container each time it was opened. The primary endpoint was daily adherence. The intervention group had a mean daily adherence of 96.8 percent which was significantly higher than 87.2 percent mean daily adherence in the control group. However, overall adherence between the two groups was not statistically significant though the intervention group was higher than the control group (97.9 percent and 90.5 percent, respectively). None of the subjects in the intervention group had a daily or overall adherence below 80 percent. Five subjects in the control group (21 percent) had an overall adherence below 80 percent, and six subjects (25 percent) showed daily adherence less than 80 percent.

This study shows that intense, individualized pharmaceutical care, including patient education, has the potential to improve daily adherence to medications. With many oral chemotherapeutic agents available today, pharmacists have the ability to maximize patient therapy while minimizing compliance-related treatment failure.

Improvement of Pharmacists' Management of Chemotherapy Side Effects

Limitations must be overcome to optimize pharmacists' management of chemotherapy side effects. Due to underuse of health information technology (HIT), fragmented health care is a common concern for all patients and can be especially troublesome for oncology patients.[18,19] HIT consists of a variety of ways to transmit health information electronically among patients, health care professionals, payers and insurers. Promoting national use of electronic health records (EHR), personal health records (PHR) and clinical data exchanges would create a continuum of care for patients allowing health care professionals nationwide to have access to a patient's entire health record when needed. When dispensing medications to patients in a community setting, pharmacists could be sure a complete drug utilization review is conducted and all aspects of a patient's chemotherapy regimen, including side effects and drug-drug interactions are addressed. Ensuring pharmacists who directly interact with patients are properly informed of patients' medical history creates an opportunity for increased patient education regarding treatment side effects and improvement in chemotherapy adherence.

Conclusion

Through increased management of supportive care, community pharmacists can decrease patient incidence of debilitating side effects. Recognizing these side effects, recommending drug therapy and educating patients on proper management allows for optimal anticancer therapy. While limitations to patient information exist, pharmacist involvement not only improves patients' quality of life, it allows for the best chance possible to fight their disease.

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Assessment Questions

1. Which is NOT a common chemotherapy-induced side effect?
    a. Nausea
    b. Constipation
    c. Loss of sight
    d. Anemia

2. Which is NOT a common sign or symptom of anemia?
    a. Dizziness
    b. Fatigue
    c. Shortness of breath
    d. Clubbing of fingers

3. All of the following are typical in patients suffering from neuropathy associated with chemotherapy EXCEPT:
    a. Neurotoxicity is often dependent on the cumulative dose of the treatment
    b. Severity of neuropathy increases with the duration of treatment
    c. Progression of neuropathy is halted with termination of treatment
    d. A diagnosis of neuropathy is made using clinical lab values

4. Which oral chemotherapy agent is mismatched with one of its common side effects?
    a. Methotrexate; CINV
    b. Erlotinib; neuropathy
    c. Lapatinib; diarrhea
    d. Sunitinib; anemia

5. What are the antiemetic medications required for a patient receiving highly emetogenic chemotherapy?
    a. 5-HT_3 serotonin receptor antagonist, dexamethasone, and aprepitant
    b. 5-HT_3 serotonin receptor antagonist and dexamethasone
    c. Only non-pharmacologic treatment is warranted at this time
    d. 5-HT_3 serotonin receptor antagonist

6. What pharmacologic intervention is appropriate for a patient suffering from grade 2 diarrhea?
    a. Administer octreotide
    b. Administer standard dose of loperamide
    c. Use of prophylactic antibiotics
    d. Increase of lactulose containing products

7. What non-pharmacologic suggestions should NOT be made to patients suffering from CINV?
    a. Wear loose fitting clothing
    b. Eat small, frequent meals
    c. Increase intake of sweet, fatty, high-salt, or spicy foods
    d. Eat ice cubes before meals

8. What non-pharmacologic suggestions should be made to patients taking chemotherapy agents prone to causing neutropenia?
    a. Explain the signs and symptoms of infection
    b. Instruct patients to practice good hygiene
    c. Instruct patients to avoid large crowded areas
    d. All of the above

9. What resources are available to aid in patient education and monitoring of chemotherapy agents?
    a. NCCN Clinical Practice Guidelines in Oncology
    b. ASCO website
    c. Board certified clinical oncology pharmacist
    d. All of the above

10. A common limitation of community pharmacists' management of patient side effects is:
    a. The underuse of HIT
    b. Too much patient information
    c. Limited access to patients
    d. Easy access to patient lab values

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Program Title: **Impact of Community Pharmacists on Management of Cancer Chemotherapy and the Resulting Side Effects**
UAN: 0048-0000-12-032-H01-P CEUs: 0.1

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Program Content:	**Strongly Disagree**				**Strongly Agree**
The program objectives were clear.	**1**	**2**	**3**	**4**	**5**
The program met the stated goals and objectives:					
Identify the most common chemotherapy-induced side effects and associated signs and symptoms.	**1**	**2**	**3**	**4**	**5**
Identify commonly dispensed oral chemotherapy agents associated with chemotherapy-induced side effects.	**1**	**2**	**3**	**4**	**5**
State possible pharmacologic treatments for the most common chemotherapy-induced side effects.	**1**	**2**	**3**	**4**	**5**
Recognize non-pharmacologic ways in which community pharmacists can help manage chemotherapy-induced side effects.	**1**	**2**	**3**	**4**	**5**
Identify resources available to community pharmacists to help manage chemotherapy-induced side effects.	**1**	**2**	**3**	**4**	**5**
Recognize common limitations prohibiting community pharmacists from being able to manage chemotherapy-induced side effects.	**1**	**2**	**3**	**4**	**5**
The program met your educational needs.	**1**	**2**	**3**	**4**	**5**
Content of the program was interesting.	**1**	**2**	**3**	**4**	**5**
Material presented was relevant to my practice.	**1**	**2**	**3**	**4**	**5**

Comment/Suggestions for future programs:

_____

_____

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C D	**4. A B C D**	**7. A B C D**	**10. A B C D**
2. A B C D	**5. A B C D**	**8. A B C D**	
3. A B C D	**6. A B C D**	**9. A B C D**	

Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, Advanced Administrative Assistant for the Office of Continuing Education (email: l-bedford@onu.edu, phone 419-772-1871).

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Lysteda® for Heavy Menstrual Bleeding

Erica B. Schoenberger, fifth-year pharmacy student from Upper Sandusky, Ohio; Todd A. Tucker Jr., fourth-year pharmacy student from Barnesville, Ohio; Justin W. Steele, fourth-year pharmacy student from Canton, Ohio; Amanda Meyer, fifth-year pharmacy student from Dublin, Ohio; **Sandra L. Hrometz**, BSPh '94, R.Ph., Ph.D., professor of pharmacology

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-12-031-H01-P

Objectives

1. Describe the mechanism of action of Lysteda®.
2. Compare and contrast treatment options for heavy menstrual bleeding.
3. List the side effects and warnings associated with Lysteda®.
4. Explain important patient counseling information.

Abstract

Lysteda®, a novel formulation of tranexamic acid, is an antifibrinolytic medication recently approved by the Food and Drug Administration (FDA) for the treatment of heavy menstrual bleeding. Tranexamic acid has been shown to significantly reduce menstrual blood loss while simultaneously allowing a woman to safely become pregnant. The major advantage of Lysteda® (an oral modified-release formulation of tranexamic acid) compared to oral immediate-release tranexamic acid, is the decreased occurrence of gastrointestinal side effects. As there are no therapeutic equivalents to Lysteda® for heavy menstrual bleeding, it is important for pharmacists to be able to counsel patients appropriately on the specific dosing regimen and side effects of this new product.

Introduction

During normal menstruation women lose approximately 35-45 mL of blood every 21 to 35 days. The amount of blood lost with each menstrual cycle varies between women and throughout an individual's life.[1] The American Congress of Obstetricians and Gynecologists define menorrhagia, or heavy menstrual bleeding (HMB), as the "loss of 80 mL or more of blood per cycle or bleeding that lasts for more than seven days," however it can also be diagnosed based on a patient's perception of excessive bleeding and interference with physical, social, and/or emotional quality of life.[2,3] Lysteda® (Ferring Pharmaceuticals Inc., Parsippany, N.J.) is the only non-hormonal medication approved to treat cyclic HMB in the United States.[4] Immediate-release tranexamic acid (TA) has been utilized in Europe, Canada, Asia and Australia for over 30 years to decrease menstrual blood loss, and it is even available over-the-counter in select countries.[4,5] The antifibrinolytic, Lysteda®, made its debut on the U.S. market in July 2010. With approximately 27 percent of women experiencing a decreased quality of life due to HMB, Lysteda® has the potential to greatly impact a significant number of women.[4] To differentiate the modified- and immediate-release forms of tranexamic acid, we will refer to the modified-release form as Lysteda® and the immediate-release form as TA throughout the remainder of this article.

Pathophysiology

Fibrinolysis, or dissolution of a clot, begins when endothelial cells release tissue plasminogen activator (tPA).[6] TPA facilitates the binding of plasminogen to lysine binding sites on fibrin, resulting in the conversion of plasminogen to plasmin. Plasmin is ultimately responsible for degrading clots, and in the uterus, the result is menstrual bleeding. Regulatory mechanisms usually control fibrinolysis, but when they fail, excessive uterine fibrinolysis may occur and lead to HMB. Tranexamic acid, a synthetic lysine analog, decreases menstrual blood loss by reversibly blocking the lysine binding site on plasminogen, preventing the formation of plasmin and subsequent fibrinolysis. HMB may be due to a specific biological cause such as uterine polyps, fibroids, endometriosis, von Willebrand's disease or hemophilia; however, half of all women with HMB suffer from idiopathic HMB. Idiopathic HMB is attributed to elevated levels of endometrial tPA and plasmin compared to women with normal bleeding, making antifibrinolytic medications such as Lysteda® an ideal treatment option.

Review of Other Treatment Options for HMB

Lysteda® is a unique and effective way of treating menorrhagia. However, because this non-hormonal treatment option was recently FDA approved and is the first of its kind, many health care professionals may not feel comfortable counseling patients on this new medication. With Lysteda® costing nearly $170 for a five day supply of 30 tablets, physicians and patients must consider the price of Lysteda® compared to more traditional medications.[7] The unique qualities of Lysteda® may be worth the price in patients who refuse, have failed or cannot tolerate traditional therapies.

One of the first questions considered upon treating menorrhagia is whether the woman wishes to preserve long-term fertility. If she does not wish to preserve long-term fertility, she may consider one of two primary surgical procedures: hysterectomy or endometrial ablation.[8] Hysterectomies are becoming much less common as second-generation endometrial ablation becomes more advanced.[9] These surgical procedures are very effective for menorrhagia, but are becoming less practical as medications become more effective, while providing the opportunity for continued fertility.

If a woman wishes to preserve her fertility long term, hormonal therapy (including hormonal contraceptives or cyclic

progesterone) and non-steroidal anti-inflammatory drugs (NSAIDs) are traditional options.

It has been long established that the best nonsurgical treatment option for HMB is the levonorgestrel-containing intrauterine device (LNG-IUD).[8,10,11] It ranks higher than all other medical treatments when considering effectiveness, side effects and length of treatment.[11] The LNG-IUD is the first-line therapy in treating menorrhagia as outlined by Britain's National Institute for Health and Clinical Excellence (NICE) guidelines for HMB released in January of 2007.[10] Women must be fitted for the IUD by a doctor or specially trained nurse and, after insertion, the IUD should be replaced every five years. This system works by releasing 20 mcg of levonorgestrel, a synthetic progesterone, every 24 hours.[1] This product suppresses endometrial growth, which causes endometrial glands to atrophy.[8] Some irregular spotting may occur within the first few months and approximately 25 percent of users develop amenorrhea, but overall patient satisfaction is high.[1,13] There is a small chance of uterine perforation at the time of placement. Common side effects include headache, breast tenderness and acne.[12,13]

Combined hormonal contraceptives (CHCs) reduce menstrual blood loss by approximately 40 percent.[8,9] On March 14, 2012, the four-phase oral contraceptive Natazia® (estradiol valerate and estradiol valerate/dienogest), became the first and only FDA approved CHC for the treatment of HMB.[14] CHCs are administered in either a cyclic or continuous manner and, like LNG-IUDs, they prevent proliferation of the endometrium.[8,9,12] Continuous administration products (meaning no inert or hormone-free interval) may improve bleeding patterns and other symptoms associated with menstruation, but the patient may also experience some breakthrough bleeding.[8,9] Although these drugs generally do not appear to pose a risk with long-term use, it should be noted that they are not recommended in some patient populations, such as smokers older than 35 years, as they increase the risk of venous thromboembolism, stroke or heart attack.[1,8,10] Common side effects associated with CHCs include headache, mood changes, nausea, fluid retention and breast tenderness.[12]

Like the other hormonal options, cyclically administered oral progestins prevent the proliferation of the endometrium and may cause amenorrhea, which may be a desired effect in patients with HMB.[9,13] Although the cyclically administered oral progestins are not FDA-labeled contraceptives, they may affect a woman's ability to become pregnant. Progestins may result in weight gain, bloating, breast tenderness, headaches, acne and, possibly, depression.[13]

Many women will initially attempt to treat heavy and painful periods on their own, making NSAIDS a popular choice. NSAIDs are the most common medications used for HMB in women who do not want hormone therapy or wish to become pregnant. By inhibiting the formation of Prostaglandins E and I_2, which appear to be elevated during menstruation and endometrial shedding, NSAIDs are able to reduce blood flow.[1] Another benefit of NSAIDs is the additional analgesia properties they provide. Because NSAIDs are only taken during menstruation, the gastrointestinal side effects commonly associated with long-term NSAID use are of little concern. Clinical efficacy between different NSAIDs appears to be similar.[8] According to the NICE guidelines, NSAIDs are preferred over TA in patients experiencing HMB with dysmenorrhea, due to the cost and analgesic effects.[12] However, Lysteda® is an option for HMB in women wishing to avoid hormonal therapy and either cannot tolerate or are refractory to NSAID therapy.

Efficacy of Tranexamic Acid and Clinical Trials

In regards to efficacy, clinical trials performed by Lukes, et al. and Freeman, et al. have demonstrated favorable outcomes in terms of the ability of Lysteda® to both reduce menstrual blood loss and improve quality of life in women suffering from HMB.[3,15] In 2010, a double-blind, randomized con-

Table 1. Treatment Options for HMB.[3,10,12]

SURGICAL					
Procedure			**Decrease in Bleeding (%)**	**Eliminate long-term fertility**	**Contraceptive Action**
Hysterectomy			100	Yes	--------
Endometrial Ablation			80-94	Yes	--------
PHARMACOLOGICAL					
Type	**Class**	**NICE Guidelines**	**Decrease in Bleeding (%)**	**Eliminate long-term fertility**	**Contraceptive Action**
Hormonal	LNG-IUD	1st Line	79-97	No	Yes
	Oral Progestin	3rd Line	87	No	Possible
	COCs	2nd Line	20-50	No	Yes
	GnRH analogues	Other	>90	No	No
Non-hormonal	NSAIDs	2nd Line	20-50	No	No
	Tranexamic Acid	2nd Line	20-60	No	No
	Lysteda®	N/A	40	No	No

trolled trial conducted by Lukes, et al. evaluated the effects of TA in adult women with HMB.[3] Women free of uterine abnormalities experiencing an average blood loss of at least 80 mL per menstrual cycle were randomized to receive either 3.9 g/day TA or placebo. Participating women received treatment at the onset of menses for up to five days each menstrual cycle and were studied over the course of six cycles. Menstrual blood was collected and measured to determine a mean reduction in blood loss. Furthermore, improvements in quality of life were assessed based on participant responses to the Menorrhagia Impact Questionnaire (MIQ), a six-question questionnaire designed to evaluate HMB-related limitations on daily activities and detect patient perceived changes in blood loss.

At the conclusion of the trial, a significant reduction in menstrual blood loss in the modified intent-to-treat population (-69.6 mL; -40.4 percent) as compared to placebo (-12.6 mL; -8.2 percent; $p<0.001$) was found. Furthermore, researchers found a significant reduction in MIQ scores on limitation in social, leisure and physical activities in the TA group compared to placebo ($p<0.001$). However, it should be noted that the study was five participants short of meeting power, as there were only 115 participants in the modified intent-to-treat receiving TA instead of the calculated 120 participants.

Similar results were found in an analogous study performed by Freeman, et al. in which women with an average menstrual blood loss of at least 80 mL per cycle were randomized to receive either 3.9 g/day TA or placebo.[15] By the conclusion of the trial, the modified intent-to-treat population consisted of 112 subjects in the treatment group and 67 subjects in the placebo group, which was sufficient to meet power. In terms of results, experimenters found a 38.6 percent (-65.3 mL) reduction from baseline in menstrual blood loss in participants receiving TA compared to placebo (-1.9 percent; -3.0 mL; $p<0.0001$).

Long-Term Safety and Health-Related Quality of Life

The long-term safety and health-related quality of life (HRQoL) of Lysteda® was examined in a multi-center, open-label trial lasting 27 months (HRQoL evaluated during the first 15 months) and included 62 sites within the United States.[16] Patients aged 18 to 49 years old with a history of HMB were diagnosed with HMB based on the medical judgment of study investigators. The intent-to-treat population included 723 patients, with 239 patients completing all 27 months. The most common reasons for withdrawing from the study were not related to the treatment (29 percent failed to return and 22 percent had unrelated requests). Eleven percent of patients reported treatment-emergent adverse effects (TEAEs) that the investigators considered related to Lysteda®. Gastrointestinal side effects were reported by 102 patients and no patients developed a venous thromboembolism (VTE) or pulmonary embolism (PE) during the study. Serious TEAEs were reported by 28 women and two women had life-threatening TEAEs, however the two events were related to other health issues and not Lysteda®. Fourteen women became pregnant and no fetal abnormalities occurred in full-term infants. During the study, 82 women reported eye issues, but only one patient had to withdraw due to severe blurred vision, which completely returned to normal upon discontinuation of Lysteda®.

HRQoL was measured using the Short Form 36 Health Survey (SF-36), a general health assessment tool, and the Ruta Menorrhagia Questionnaire (RMQ), a disease specific tool. Both showed statistically and clinically significant improvements mentally, emotionally and physically starting with the first cycle of treatment and persisting throughout treatment.

This study had a few major drawbacks. First of all, the investigators subjectively determined causality between the adverse effects and medication use. Secondly, they decided the significance of reported adverse events, resulting in possibly biased results. Finally, they did not report the number of patients included in the 15 month HRQoL portion of the study. Overall, this study concluded that gastrointestinal issues with Lysteda® occur at rates lower than reported with TA and demonstrated no increased risk of developing thromboembolism due to Lysteda® use, however there is a small risk of serious ophthalmic issues.

Pharmacist Information and Patient Counseling

The main advantage of Lysteda® over TA is a decreased occurrence of gastrointestinal side effects such as nausea, vomiting, diarrhea and dyspepsia, resulting in greater tolerability and patient compliance.[16] The most common side effects reported with Lysteda® are those associated with menstruation, including menstrual discomfort, headache and back pain.[17] However, these side effects may be reduced with concurrent use of acetaminophen, ibuprofen or naproxen.[17] The most serious adverse effects possible with Lysteda® are thromboembolisms and ocular disturbances. To avoid an excessive risk of thrombosis, it is contraindicated in patients with active, history of, or other risk factors for thromboembolism.[18] Additionally, Lysteda® should not be used concomitantly with CHCs or hormone replacement therapy.[17] It is also important to warn patients of possible visual changes which will reverse upon discontinuation of the medication.

The recommended dosage of Lysteda® is 1300 mg (two 650 mg tablets) taken three times per day, with doses separated by six hours.[4,17] It can be taken with or without food.[18] Dose adjustments are required in patients with a serum creatinine greater than 1.4 mg/dL (Table 2).[18] Women should be instructed to begin taking Lysteda® at the onset of menses, and continue use for a maximum of five days throughout menstruation. Since Lysteda® is only intended to be taken during menstruation, pharmacists should remind patients not to take it continuously throughout the month, as is common with other treatments.

Finally, since patients may confuse Lysteda® with more traditional hormonal treatments for HMB, pharmacists should explain that Lysteda® is a non-hormonal medication and has no effect on fertility.[4] Therefore, women may become pregnant and should be instructed to use barrier forms of contraception if necessary. Other counseling points include educat-

Table 2. Renal Dose Adjustments for Lysteda®[18]

Serum Creatinine (mg/dL)	Dosing
≤1.4	1300 mg TID
1.5 – 2.8	1300 mg BID
2.9 – 5.7	1300 mg daily
≥ 5.8	650 mg daily

ing women on ways to manage premenstrual symptoms, such as drinking plenty of water, getting adequate rest and avoiding excessive salt and caffeine intake.

Conclusion

Heavy menstrual bleeding is a troublesome condition that interferes with the lives of approximately 27 percent of women. To date, there are several treatment options available to reduce bleeding, such as hormones, NSAIDS, Lysteda® and surgery in severe cases. The non-hormonal Lysteda® may help women effectively reduce menstrual bleeding without interfering with the ability to conceive. With Lysteda®, women can expect to see an approximate 40 percent reduction in bleeding while experiencing only the mild side effects associated with menstruation. Furthermore, Lysteda® has demonstrated a favorable safety profile and has not been associated with any serious adverse events. Since it was only recently introduced to the U.S. market in July 2010, much of the medical community remains unfamiliar with Lysteda®; however, it is an additional, effective, non-hormonal treatment option for women suffering from HMB.

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Assessment Questions

1. Idiopathic heavy menstrual bleeding (HMB) is due to:
    a. Excessive fibrin
    b. Reduced lysine
    c. Intrauterine devices (IUDs)
    d. Elevated endometrial tPA and plasmin

2. Lysteda® reduces menstrual blood loss by:
    a. Blocking lysine binding sites on plasminogen
    b. Preventing synthesis of lysine
    c. Increasing plasmin levels
    d. Reducing endometrial tPA

3. Lysteda can treat HMB caused by :
    a. Idiopathic causes
    b. Endometriosis
    c. von Willebrand's disease
    d. A and B
    e. B and C

4. The most effective non-surgical treatment for HMB is:
    a. Natazia®
    b. Levonorgestrel-containing intrauterine device (LNG-IUD)
    c. Lysteda®
    d. Ibuprofen

5. FDA approved treatment options for HMB include:
    a. Lysteda®
    b. Natazia®
    c. Advil®
    d. A and B
    e. All of the above

6. Lysteda reduced menstrual blood flow by approximately____.
    a. 20%
    b. 40%
    c. 60%
    d. 80%

7. What is the major advantage of Lysteda® over tranexamic acid?
    a. Increased effectiveness
    b. Reduced side effects
    c. Easier administration
    d. Reduced menstrual cramping

8. What serious side effect(s) is a concern with Lysteda®?
    a. Amenorrhea
    b. Ophthalmic issues
    c. Nausea and vomiting
    d. A and C

9. What is the recommended dose of Lysteda® in a young, healthy female?
    a. 650 mg daily
    b. 1300 mg daily for 21 days
    c. 1300 mg TID for a maximum of 5 days
    d. 1300 mg as needed for heavy menstruation

10. Lysteda® can safely be taken concomitantly with which medication(s)?
    a. Advil®
    b. Lo Loestrin Fe®
    c. Premarin®
    d. B and C
    e. All of the above

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Program Title: **Lysteda® for Heavy Menstrual Bleeding**
UAN: 0048-0000-12-031-H01-P CEUs: 0.1

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Program Content:	**Strongly Disagree**				**Strongly Agree**
The program objectives were clear.	**1**	**2**	**3**	**4**	**5**
The program met the stated goals and objectives:					
Describe the mechanism of action of Lysteda®.	**1**	**2**	**3**	**4**	**5**
Compare and contrast treatment options for heavy menstrual bleeding.	**1**	**2**	**3**	**4**	**5**
List the side effects and warnings associated with Lysteda®.	**1**	**2**	**3**	**4**	**5**
Explain important patient counseling information.	**1**	**2**	**3**	**4**	**5**
The program met your educational needs.	**1**	**2**	**3**	**4**	**5**
Content of the program was interesting.	**1**	**2**	**3**	**4**	**5**
Material presented was relevant to my practice.	**1**	**2**	**3**	**4**	**5**

Comment/Suggestions for future programs:

_____

_____

_____

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C D	**4. A B C D**	**7. A B C D**
2. A B C D	**5. A B C D E**	**8. A B C D**
3. A B C D E	**6. A B C D**	**9. A B C D**

10. A B C D E

Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, Advanced Administrative Assistant for the Office of Continuing Education (email: l-bedford@onu.edu, phone 419-772-1871).

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Laboratory Mutations of H5N1 Confer Efficient Transmission in Animal Models and Generate International Debate Regarding Publication of Dual Use Research

Morgan A. Belling, fourth-year pharmacy student from Rochelle, Ill.; Kelly Dye, fourth-year pharmacy student from Kennerdell, Pa.; Joshua Ilenin, fifth-year pharmacy student from Mantua, Ohio; Jamie Amero, fifth-year pharmacy student from Boardman, Ohio; **Andrew Roecker**, PharmD '00, BCPS, associate professor of pharmacy practice

Abstract

H5N1, a subtype of influenza A virus that originated in Hong Kong in 1997 and has since spread across Asia and Africa, features a reported case fatality rate of nearly 60 percent in humans. Although naturally-occurring H5N1 has not developed the ability to be efficiently transmitted from human to human, two independent research teams have recently mutated strains of the virus, resulting in facile transmission among laboratory ferrets, which are considered the most accurate models for humans in viral studies. As a consequence of the security and public health risks of such information, the U.S. National Science Advisory Board for Biosecurity recommended that *Science* and *Nature* refrain from publishing full versions of the research manuscripts. The move has provided a platform for international debate as scientists assess the potential benefits and hazards as a consequence of either disseminating all details of the studies or only a select few.

Introduction

The possibility of a major influenza pandemic represents a significant threat to the livelihood of people around the world. Influenza pandemics usually occur when a new strain of influenza, to which the population lacks immunity, can spread more quickly and infect larger numbers of people than the seasonal influenza virus.[1] Recently, the H5N1 subtype of influenza has been of major concern. H5N1 is an extremely virulent form of avian influenza that has developed the ability to infect humans.[2] The first recorded case of human infection with H5N1 occurred in Hong Kong, China, during 1997. The virus became widespread during 2003 and 2004, with reported cases stretching from Asia to Africa.[3,4] As the virus continues to spread farther across the globe, and the possibility of mutations exists, the threat to public health continues to increase significantly.

Descriptions of the clinical course for this virus are predominantly based on case reports from patients hospitalized with H5N1 infections. Patients commonly present with a fever of greater than 38°C and other symptoms similar to more common influenza strains such as diarrhea, vomiting, chest or abdominal pain, as well as non-traditional symptoms, including bleeding from the nose or gums.[2,3] One distinguishing characteristic of H5N1 infection from other strains of influenza may be the incubation period prior to presentation of symptoms. H5N1 has been shown to have an incubation period of two to eight days compared to two to three days for common influenza strains. Risk factors for contracting H5N1 appear to largely be contained to exposure to infected poultry or an environmental fomite that may have been in contact with infected fowl.[2] There is little evidence to suggest that individuals can become infected by consuming poultry that has been properly cooked or prepared or from everyday human-to-human contact if appropriate precautions are taken.[2,3] Due to the similar symptomology with other strains of influenza, appropriate lab tests such as H5-specific RNA or viral isolation are required for definitive H5N1 diagnosis.[3]

The majority of epidemiologic data related to H5N1 are also derived from patient case reports, most of which originate from countries across Africa and Asia, where H5N1 has spread since the initial human case in China in 1997.[3,4] As of 2012, a total of 583 confirmed human cases have been reported to the World Health Organization (WHO), resulting in 344 deaths associated with the virus.[5] The extremely high case fatality rate associated with H5N1 makes identifying appropriate drug therapy options to treat infected patients paramount. However, due to the small number of human H5N1 cases, no randomized clinical trials have been conducted to identify the preferred treatment.[6] Currently, the treatment of choice is an oral neuraminidase inhibitor such as oseltamivir (Tamiflu®).[3,6] Neuraminidase inhibitors block the release of new viral particles from infected host cells, thereby preventing the propagation of influenza virus within the host.[7] In an attempt to develop a formalized treatment guideline for H5N1, the WHO recommended that the seasonal influenza treatment regimen of oseltamivir 75 mg twice daily for five days be used for H5N1 as well.[6] However, researchers have suggested that higher doses may be necessary to adequately treat such a virulent strain of influenza.[3,6] All patients with suspected H5N1 infections should be hospitalized in isolation to reduce the risk of spread to other individuals.[3] Despite clinicians' best efforts to treat H5N1 with currently available antiviral drugs, resistance to oseltamivir therapy and overall mortality remain high. Given the lack of effective treatment, the development of natural or laboratory-induced mutations that allow for extensive human-to-human transmission is a major concern.

Humans possess several defense mechanisms to combat the possibility of infection with influenza. Therefore, a pandemic involving H5N1 may be closely linked to the development of several specific mutations that lead to greater transmissibility in humans.[8] One such mutation, found in the polymerase complex of viral genes, allows for increased replication of the virus in human tissue. Laboratory analysis of H5N1 isolates has shown that this mutation may already be present in the virus, representing a major step toward pandemic potential.

However, without the presence of an additional mutation in the amino acid sequence that codes for the hemagglutinin (HA) protein of the avian virus, allowing it to bind more easily to cells in the human respiratory tract, the likelihood of a large-scale pandemic and human-to-human viral transmission remains low.[8] To date, none of the naturally occurring mutations in viral HA have resulted in widespread human-to-human transmission. Concerns regarding the development of such mutations artificially in a laboratory setting and the subsequent publishing of data have been a major topic of recent discussions in the scientific community.

Current Discussions

Twenty H5N1 clades, all sharing the H5 hemagglutinin (HA) gene but otherwise differing in genotype as a result of evolutionary processes, have been identified and classified since 2008; although these naturally-occurring strains of H5N1 are not currently easily transmissible among humans, prominent influenza research teams led by Dr. Yoshihiro Kawaoka at the University of Wisconsin-Madison and the University of Tokyo and Dr. Ron Fouchier at Erasmus Medical Center in Rotterdam, the Netherlands, have independently developed genetically mutated variants whose alterations impart efficient spreading of the virus in ferrets, the laboratory animals considered to be the most accurate models of humans in studies of viral transmission and virulence.[9-11] Genetically modified H5N1 strains possessing an altered HA protein were able to spread rapidly among the rodents and the viruses in Fouchier's studies proved particularly lethal, a trait also observed in the viruses produced by Kawaoka's team, albeit to a lesser extent.[11] These discoveries may advance the scientific community's understanding of the mechanisms by which viruses gain the ability to spread from human to human, as the present lack of details of such pathogenesis represents a significant obstacle in preventing possible pandemics.[10]

The information from these studies would allow researchers to investigate preemptive means to decrease the risk of transmission of the virus among humans, including the development of more advanced vaccines and surveillance protocols and delineation of appropriate countermeasures. For these reasons, the researchers submitted manuscripts of their work to the journals *Nature* and *Science* in late 2011.[12] In response to the sensitive content of the papers, the U.S. National Science Advisory Board for Biosecurity (NSABB) requested on December 20, 2011, that the journals censor certain components of the articles.[11,13,14] The NSABB, established in 2004 as a result of the 2001 anthrax bioattacks in the eastern part of the United States, serves as a "federal advisory committee chartered to provide advice, guidance and leadership regarding biosecurity oversight of dual use research, defined as biological research with legitimate scientific purpose that may be misused to pose a biologic threat to public health and/or national security."[13] The board, currently chaired by microbiologist Paul Keim of Northern Arizona University, made the unprecedented recommendation that *Nature* and *Science* publish the conclusions of the submitted manuscripts but refrain from including "the methodological and other details that could enable replication of the experiments by those who would seek to do harm."[14] The move has since sparked intense debate among members of the scientific, security and public health communities.

Realizing the complexity of the multiple perspectives of those involved, both Kawaoka and Fouchier announced on January 20, 2012, that for 60 days, their laboratories would voluntarily postpone their research regarding experimental mutations that confer transmission among mammals and involve live H5N1 or H5 HA reassortant viruses previously observed to be transmissible in ferrets but would continue to study naturally occurring strains.[10] This halt would allow time for international forums to discuss the implications of publication or lack thereof of the studies. In mid-February 2012, 22 scientists and personnel of *Nature* and *Science* convened in Geneva, ultimately deciding that partial publication of the studies would not be beneficial to further research and extending the moratorium on investigation of laboratory-developed H5N1 strains.[12]

Scientific Review Process

One key component of international discussion of this issue is how sensitive material in medical literature is scrutinized and considered for publication by the NSABB. The NSABB is responsible for many tasks, including providing guidelines for the identification, review, conduction and communication of dual use research.[15] These guidelines can be found in the NSABB publication "Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information."[16] One specific purpose of the NSABB is to "advise on policies governing publication, public communication and dissemination of dual use research methodologies and results."[16] In summary, the NSABB committee analyzes the risks and benefits of dual use research and formulates a recommendation on proper dissemination of the material based on content, timing and distribution.[15] The NSABB aims to consider both the importance of the advancement within the scientific community as well as the concerns of national security, particularly minimizing the risk of the misuse of said information.[15]

In regard to the H5N1 experiments conducted by Kawaoka and Fouchier, the NSABB analyzed the researchers' two scientific papers concerning the respiratory transmission of the virus from mammal to mammal. After meeting with several experts in the field of influenza research and public health, NSABB personnel determined that the potential benefits of publishing the research did not outweigh the possible negative consequences associated with disseminating complete versions of the manuscripts. The NSABB's recommendation to *Science* and *Nature* to refrain from publishing the methodology of the studies so it could not be duplicated while still allowing the publication of other scientifically relevant information was also endorsed by the National Institutes of Health (NIH), which provided a portion of the research funding.[11] Specifically, NSABB asked that details related to the specific amino acid changes that lead to the virus's transmissibility be removed.[17] Government bodies, including the NIH's National Institute of Allergy and Infectious Diseases (NIAID) and the WHO, have also contributed to the discussion, as well as news media such as National Public Radio

(NPR), which facilitate microcosms of needed forums.

A virus as lethal as H5N1, which has a documented case fatality rate of nearly 60 percent in humans who have contracted the disease, is one to be handled with constant vigilance and the utmost care, especially when that virus has been modified in the laboratory to impart efficient transmission among animals that are considered the prototypical model for pathology in humans.[5,17,18] NSABB board members and other advisory personnel emphasize such facts as supporting evidence for the request for censorship. The suggestion has been made that full versions of the papers be selectively distributed so that only approved personnel investigating the H5N1 virus have access to "dual use" information.[12] However, ensuring the integrity of the means by which the manuscripts are promulgated is a process without current clarity.

Alternatively, researchers argue that it is highly unlikely that a ferret-adapted influenza virus could be used for bioterrorism.[19] For instance, knowing the amino acid changes required for transmission in the ferret does not directly enable the production of a biological weapon.[19] Furthermore, many live attenuated vaccines have been produced by using animals models, including ferrets, and the benefits of releasing the information for this purpose have proven to be vast.[19,20] Other proponents state that it is also unknown whether a virus that will replicate in and transmit among ferrets would possess the same abilities in humans.[20] Therefore, one cannot directly extrapolate this data to make predictions about a human host. While some scientists cite academic freedom as the primary reason to fully disseminate the information, others advocate for the potential advances in the understanding of virology and preventing or controlling such devastating pathogens that could result from unabridged publication.

In contrast, others contend that the decision to leave out key information in the methodology was the correct form of action. This virus is highly lethal in humans, more so than the influenza virus responsible for the 1918 pandemic that killed 50 million people, and if a strain gained efficient human-to-human transmission, the consequences could be severe.[21] Recently, Keim discussed his reasoning behind the NSABB recommendation. He stated that the committee "carefully considered how restricting the information would compromise scientific research progress and even how it would hinder public health efforts to prevent such a horrific pandemic."[22] He also asserted that "the short term negative consequences of restricting experimental details seemed small in contrast to the large consequences of facilitating the replication of these experiments by someone with nefarious intent."[22] Keim also noted that the NSABB consists of actively practicing scientists who agree with the promotion of the publication of scientific research and that "the recommendation not to publish scientific results was highly unusual and the first such recommendation by the NSABB membership."[22] Following the guidelines set by the NSABB, they determined that the research had the potential to be dangerous and recommended the restriction of the publication of the manuscripts.

Conclusion

As researchers continue discussions, both the WHO and the U.S. government are working to develop policies and guidelines for the distribution of restricted information. Balancing scientific discovery and medical advancement with potential threats to public safety is a contentious issue that harbors significant, widespread implications; much progress is needed to ensure that the world's population is protected not only from naturally-occurring pathogens but also from those developed by individuals who seek to manipulate such viruses for bioterrorism.

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Dronedarone: An Update to a Controversial Therapy for Atrial Fibrillation

Zachary Crawford, fourth-year pharmacy student from Centerville, Ohio; Sara McAllister, fourth-year pharmacy student from Youngstown, Ohio; Amanda Hoersten, fifth-year pharmacy student from Delphos, Ohio; Jennifer Bauer, fifth-year pharmacy student from St. Marys, Pa; **Megan Keller**, PharmD '11, community pharmacy resident; David Bright, PharmD, BCACP, assistant professor of pharmacy practice

Abstract

As of 2004, it was estimated that 2.2 million Americans were diagnosed with paroxysmal or persistent atrial fibrillation (AF) resulting in one out of every six strokes in the United States. AF leads to a reduction in pumping efficiency of the heart increasing the risk of several serious sequelae such as thromboembolic stroke and congestive heart failure (CHF). It also results in a reduced quality of life for the patients suffering from the disease. Patients with AF require appropriate antiarrhythmic therapy to control symptoms and prevent adverse effects of the condition. Multaq® (dronedarone), an antiarrhythmic drug approved for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF, showed promise as an alternative to amiodarone therapy after its approval in July 2009. However, recent reports have shown that dronedarone use doubles mortality risk and serious adverse events in certain patient populations specifically those with heart failure or permanent AF. This review evaluates the research that brought dronedarone to the market and reassesses the appropriateness of its use based upon recent findings.

Introduction

Atrial fibrillation (AF), a supraventricular tachyarrhythmia, and associated atrial flutter are two of the most common clinically significant cardiac arrhythmias.[1-4] In 2004, an estimated 2.2 million Americans had paroxysmal or persistent AF, affecting roughly 0.4 percent of the general population, with an increased prevalence of greater than 6 percent in those over 80 years of age. Patients with non-rheumatic AF are two to seven times more likely to suffer an ischemic stroke than those without AF. Additionally, one in every six strokes occurs in a patient with AF. According to the Framingham study, overall stroke risk in patients aged 80 to 89 drastically increases to 23.5 percent from 1.5 percent in patients aged 50 to 59. While AF itself is not directly life threatening, it results in reduced pumping efficiency of the heart, which increases the risk of several serious sequelae including thromboembolic stroke and CHF. Quality of life measures in AF patients are drastically reduced due to multiple symptoms associated with the condition including palpitations, dyspnea, chest pain, fatigue and dizziness. However, these symptoms vary between patients.

To manage patients with AF, it is paramount to address the issues related to the arrhythmia itself and to strive for the prevention of a thromboembolism.[1,2,4] Management of dysrhythmias in patients with persistent AF can be done in two ways: restoration and maintenance of sinus rhythm or permitting AF to continue and ensuring the ventricular rate is controlled. Relief of symptoms, prevention of embolism and avoidance of cardiomyopathy are the main reasons for restoration and maintenance of sinus rhythm in patients with AF. Dysrhythmias can be managed pharmacologically or non-pharmacologically via electrical cardioversion, surgical or catheter ablation, pacing or with an internal atrial cardioverter/defibrillator.

Pharmacologically, the antiarrhythmic drug class is broken down into subcategories.[5] These include type I sodium channel blockers, which can be further divided into Ia, Ib, Ic according to dissociation rates from the sodium channels; type II beta adrenergic receptor antagonists; type III drugs that prolong the refractory period by prolonging the action potential; and type IV non-dihydropyridine calcium channel blockers. A specific drug or class should be chosen based on the cause of the arrhythmia, pharmacokinetics and patient-specific conditions. For more information on antiarrhythmic drug classes refer to Chapter 29: Anti-arrhythmic drugs in the twelfth edition of "Goodman and Gilman's the Pharmacological Basis of Therapeutics."[2]

One of the newer antiarrhythmics to come onto the market, dronedarone (Multaq® Sanofi U.S., Bridgewater, N.J.), was approved by the Food and Drug Administration (FDA) in July 2009 to reduce the risk of hospitalization for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF.[6-9] This drug was formulated to mimic the effects of amiodarone, a class III antiarrhythmic agent approved for the treatment of refractory life-threatening ventricular arrhythmias; however, dronedarone was intended to have an improved safety and tolerability profile compared to amiodarone. The typical adult dosage of dronedarone is 400 mg by mouth twice daily, administered as one tablet with the morning meal and one tablet with the evening meal. It should not be used in patients with permanent AF, as this use is associated with an increased risk of death, stroke and heart failure. Additionally, dronedarone carries a boxed warning contraindicating its use in patients with New York Heart Association (NYHA) class IV heart failure, patients with symptomatic heart failure with recent decompensation and in patients in AF who cannot be cardioverted into normal sinus rhythm. Recent reports have shown that dronedarone use doubles mortality risk and serious adverse events in these patient populations. The purpose of this review is to evaluate the research that brought this drug to the market and to reassess recent findings questioning the appropriateness of its use.

Clinical Trial Evaluations

The European Trial in Atrial Fibrillation or Flutter Patients

Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and The American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) trials were evaluated by the FDA for the approval of dronedarone in the United States. Additional information gathered from the ATHENA trial also supports the use of dronedarone in AF.

EURIDIS/ADONIS (2003) The results of two identical, placebo-controlled, multicenter, double-blind, parallel group trials were published in *The New England Journal of Medicine* in late 2007.[10] The objective of these trials was to assess if dronedarone was superior to placebo for maintaining sinus rhythm after electrical, pharmacologic or spontaneous conversion from AF or atrial flutter. The two trials involved in this study were EURIDIS and ADONIS. Inclusion and exclusion criteria were deemed appropriate for each study's purpose.

The participants were randomized into either the placebo group or the dronedarone group. In order to meet 90 percent power, for both EURIDIS and ADONIS, 368 patients in the dronedarone group and 184 patients in the placebo group had to complete the trial.[10] Neither trial met power due to patients discontinuing treatment prior to completion of the study. At one year, the rates of recurrence of AF were 64.1 percent in the dronedarone group and 75.2 percent in the placebo group. The researchers concluded that dronedarone reduced the incidence of a first recurrence and the incidence of a symptomatic first recurrence within 12 months of the trial start date. Some limitations of the trials include: the lack of comparison between dronedarone and other medications, resulting in the inability to compare adverse events and efficacy; the inability to detect every episode of recurrent arrhythmia; the exclusion criteria was extensive and may not be realistic in a normal practice setting; and patients who received amiodarone previously could be enrolled in the trial immediately after discontinuing the drug.

ATHENA (2008) The results of the ATHENA study were published in *The New England Journal of Medicine* in early 2009.[11] ATHENA assessed the effects of dronedarone on cardiovascular events in patients with AF or atrial flutter. The trial was a randomized, double-blind, placebo-controlled study conducted in 37 countries. Inclusion and exclusion criteria were deemed appropriate for the study's purpose.

The trial enrolled a total of 4,628 patients who were randomized to either the dronedarone group or the placebo group.[11] Out of the 2,301 patients receiving dronedarone, 734 (31.9 percent) experienced a primary outcome event (i.e., hospitalization due to cardiovascular events or death). Of the 2,327 receiving placebo, 917 (39.4 percent) had a primary outcome event. In order to meet a statistical power of 80 percent, the researchers estimated that 2,150 patients per group were necessary. This trial did not meet power due to over 30 percent of the patients in the dronedarone group and the placebo group discontinuing the trial prior to the conclusion of the study. The results of ATHENA found the use of dronedarone significantly reduced the risk of hospitalization due to cardiovascular events or death in these patients. Dronedarone was found to increase the time to first recurrence of AF from 53 days with placebo to 116 days with the active drug. Some limitations of the study including lack of comparison of dronedarone to other medications, the inability to detect every episode of recurrent arrhythmia and the large discontinuation rate of the dronedarone group (30.2 percent) may have limited the data regarding rates of adverse events (Table 1).

While studies have shown support for dronedarone in AF patients, several studies have brought its use into question, specifically in patients with heart failure and permanent AF.

Table 1. Important data from the trials supporting dronedarone[10,11]

	EURIDIS/ADONIS[10]	ATHENA[11]
Dronedarone dose	400 mg BID	400 mg BID
Primary endpoint(s)	Time from randomization to first documented recurrence of atrial fibrillation for at least 10 minutes	First hospitalization due to cardiovascular events or death
Secondary endpoints	Symptoms of atrial fibrillation, the mean ventricular rate during the first recurrence	Death from any cause, death from cardiovascular causes, hospitalization due to cardiovascular events
Number of patients randomized to dronedarone group	828	2301
Dronedarone patients who completed the trial	680	1605
Dronedarone hazard ratio	0.75	0.76
Significant inclusion criteria	≥ 21 years old, in sinus rhythm for at least 1 hour before randomization	≥ 70 years old, previous stroke, left ventricular ejection fraction ≤ 40%
Significant exclusion criteria	Permanent atrial fibrillation, NYHA class III or IV heart failure, use of other class I or III antiarrhythmics	Permanent atrial fibrillation, NYHA class IV heart failure, planned major surgery, use of other class I or II antiarrhythmics

ANDROMEDA (2003) The Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) was a multicenter, double-blind, placebo-controlled, randomized, parallel-group trial comparing dronedarone 400 mg twice daily with matching placebo.[12] This trial was conducted at 72 hospitals throughout several countries in Europe. The study aimed to enroll 1,000 patients to achieve a power of 90 percent with a two-sided type 2 error of 5 percent. The study was designed to specifically evaluate dronedarone with heart failure by enrolling patients classified as NYHA class III or IV heart failure. The trial measured adherence to the study by conducting a pill count at each study visit.

The primary endpoint was a composite of death from any cause and hospitalization for worsening heart failure while the secondary endpoints were death from all causes, hospitalization for cardiovascular causes or recurrence of AF.[12] Endpoints were considered to be cardiovascular unless an unequivocal non-cardiovascular cause was established. The study was initiated in June 2002, but terminated early by the safety committee in early 2003 due to an increase in death associated with the dronedarone group. At the time of termination, ANDROMEDA had enrolled 627 patients which was not enough to meet power. A total of 37 patients died during the study with 25 in the dronedarone group and 12 in placebo group (p=0.03). Very few patients reached 180 days of follow-up causing a small percentage of patients to be included in statistical analysis. While the number of deaths due to arrhythmia or sudden death was not different between the two groups, more participants died due to worsening heart failure with dronedarone compared to placebo (10 versus two respectively). Dronedarone also had a higher rate of hospitalization for cardiovascular related cause compared to the placebo arm (71 versus 50, p=0.02).

DIONYSOS (2008) A short-term, randomized, double-blind, parallel-group study to evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation (DIONYSOS) was published in 2010 to compare the effectiveness of dronedarone to amiodarone in patients with persistent AF.[13] The study was conducted in 112 centers in 23 countries throughout the world between 2007 and 2008. The goal of this study was to compare the benefit/risk ratio of dronedarone and amiodarone. The combined primary endpoint was defined as recurrence of AF or premature study drug discontinuation for lack of efficacy and intolerance.

Participants with documented AF for >72 hours for whom cardioversion and antiarrhythmic treatment was deemed necessary by study investigators were enrolled. A total of 472 patients were necessary to show a relative reduction in primary endpoint of 30 percent in six months in dronedarone compared to amiodarone and a power of 80 percent with a type I error of 5 percent (two-sided). The study achieved power by enrolling 504 patients. Participants were randomized to dronedarone 400 mg twice daily or amiodarone 600 mg every day for 28 days, then 200 mg every day thereafter. The results showed amiodarone may be superior to dronedarone in the conversion of persistent AF patients. AF recurrence following cardioversion was lower in the amiodarone group compared to the dronedarone group (24.3 percent vs. 36.5 percent respectively, p<0.001). While it is known amiodarone has many complications, including an interaction with warfarin and alteration of thyroid function, it may be superior for conversion in these patients. A high percentage of AF patients are taking warfarin for anticoagulation and this may pose a problem; however, warfarin dosing can be adjusted downward while taking amiodarone. It is also important to note the study used a lower dose of amiodarone (600 mg/day for 28 days, then 200 mg/day thereafter) compared to previous studies. The SAFE-T study used much higher dosing (800 mg/day PO for 14 days, then 600 mg/day for 14 days, then 300 mg/day for the first year and 200 mg/day thereafter) of amiodarone to show superiority to sotalol than the investigators of DIONYSOS used when comparing to dronedarone.[7,14] This may cause over inflation of recurrence rates of AF when using amiodarone in DIONYSOS, showing amiodarone may be even more superior to dronedarone.

PALLAS (2011) The Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) was a randomized, double-blind, placebo-controlled trial conducted in 489 centers throughout the world.[15] Patients enrolled had permanent AF documented with electrocardiography 14 days before randomization and six months earlier. The co-primary outcomes were composite of stroke, myocardial infarction, systemic embolism or death from cardiovascular cause and unplanned hospitalization for cardiovascular cause or death. For a power of 90 percent, 10,800 participants were needed for the trial. The study began in July 2010 and was terminated in July 2011 for safety reasons with a total of 3,236 patients enrolled.

At the time of study termination, the first co-primary outcome occurred in 43 participants in the dronedarone group compared to 19 in the placebo group (p=0.002). Participants in the dronedarone group also experienced more secondary outcomes, 127 versus 67 respectively (p<0.001). This significant increase in outcomes for the dronedarone arm caused the safety board to terminate the study. The dronedarone group also had a significantly higher rate of death including death from cardiovascular causes, such as arrhythmia, and higher rate of unplanned cardiovascular hospitalization compared to the placebo group.

PALLAS shows that dronedarone should not be used in patients with permanent AF due to a much higher incidence of adverse effects. It may be more important to control rate and prevent thrombosis in patients with permanent AF than to administer an antiarrhythmic. The longer a patient is in AF, the lower the chances of cardioversion with either pharmacological or non-pharmacological treatment.

Current Dronedarone Trials

The Effect of Addition of Dronedarone to Standard Rate Control Therapy on Ventricular Rate During Persistent Atrial Fibrillation (AFRODITE) is currently underway to assess

whether the addition of dronedarone to existing conventional rate control leads to a reduced ventricular rate after one week of dronedarone treatment in patients with a high heart rate at rest during AF.[16] This is a phase IV study comparing the addition of dronedarone to a beta blocker, calcium channel blocker or digoxin in an effort to reduce heart rate. The study was completed in November 2011, but data is not available at the time of this publication.

Several other studies evaluating the efficacy of dronedarone are currently underway. Dronedarone pattern of use in patients scheduled for elective cardioversion (ELECTRA) is a multi-center study in Canada evaluating patients with persistent AF who are undergoing elective cardioversion.[17] The objective of this study is to compare the rate of recurrence with dronedarone to placebo within six months. Data have not yet been released, even though the trial was expected to be completed in 2011. The effects of dronedarone on AF burden in subjects with permanent pacemakers (HESTIA) is a randomized, multicenter study to evaluate dronedarone's effects on AF burden.[18] HESTIA was terminated before study completion, but at the time of this publication data from the study have not been released.

Dronedarone and Heart Failure

Dronedarone has a black box warning for patients with NYHA class IV heart failure or recent decompensation of heart failure requiring hospitalization.[7] This contraindication was based on an increased risk of death noted in the ANDROMEDA study; however, the early termination of the study does not allow for proper evaluation of dronedarone in heart failure. It is important to note that in ANDROMEDA up to the time of termination only 19 of 627 enrolled had class IV heart failure.[12] The majority of participants had class II (252/627) and class III (356/627). Due to the early termination, it is not possible to discern which deaths from progressive heart failure were in class II, III or IV. Conversely, in the ATHENA study, 21 percent of participants had CHF with NYHA class II or III and 12 percent had LVEF <45 percent.[11] The investigators of ATHENA claim a subgroup analysis indicates patients with CHF had a similar benefit to the entire group, but due to a small population of heart failure patients, this claim lacks substantial evidence.[11] The published data of ATHENA did not provide information on outcomes specifically for participants with heart failure. Based on information from ANDROMEDA, even though dronedarone is only contraindicated for class IV heart failure, caution should be used when administering dronedarone to patients with any class of heart failure.[12]

Discussion

Dronedarone has been controversial since the ANDROMEDA study, and its safety and efficacy profile in AF therapy has not been proven. When ANDROMEDA was prematurely terminated in 2003, the sponsor and authors continued analyses on the data, searching for explanations of its findings.[12] The study was not published until 2008, after other information on dronedarone had been released and regulatory submissions were considered. Looking into the history of dronedarone, the initial new drug application (NDA) submitted in 2005 was not approved, citing poor results from ANDROMEDA as a reason.[16] Sanofi-Aventis then reapplied in 2008, using information from DIONYSOS and ATHENA in support of dronedarone.[17] While it was approved, the advisory committee recommended that patients with advanced (NYHA class III or IV) heart failure be excluded from dronedarone therapy and a black box warning be issued. However, the package insert only lists a contraindication for class IV heart failure.

This controversy places pharmacists in a pivotal role to ensure proper pharmacologic therapy for AF. Pharmacists are crucial to drug utilization reviews and ensuring patients are receiving the best pharmacological therapy. Drug utilization reviews empower and help guide pharmacists' decisions in appropriate therapy management in AF patients. Due to the increased risk of death in heart failure patients, especially those with permanent AF, pharmacists should be weary when patients with heart failure have prescriptions for dronedarone. International normalized ratio (INR) analyses from DIONYSOS showed that dronedarone did not have as significant an effect on INR levels compared to amiodarone, indicating that dronedarone should be considered for patients on warfarin with AF.[13] However, due to substantial information on adjusting warfarin dosing with amiodarone, pharmacists should not exclude using amiodarone with warfarin. Finally, it is important that pharmacists help to educate physicians and other clinicians about the possible serious consequences if dronedarone is not used properly.

AF results in an increased burden on quality of life, specifically in older patients. This population is often faced with a poor prognosis in terms of venous thromboemboli and mortality secondary to worsening comorbidities such as heart failure, coronary artery disease and hypertension. Control of AF is typically achieved through rate or rhythm control and anticoagulation. Dronedarone, a pharmacological agent used for rate control, is currently indicated to reduce the risk of hospitalization for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF. However, due to findings from the trials studied, the safety and efficacy of dronedarone is in question. ANDROMEDA showed that dronedarone should not be used in patients with NYHA class IV heart failure and may not be safe in patients with NYHA class II and III heart failure.[12] PALLAS indicated dronedarone is not safe in patients with permanent AF leading to its contraindication in such patients.[15] DIONYSOS compared dronedarone to amiodarone for use in patients with persistent AF, but showed amiodarone may be superior to dronedarone in this situation.[13] It is possible dronedarone may be used for patients with lone AF with no other complicating factors.

Conclusion

Dronedarone was approved in 2009 as an alternative to amiodarone for the treatment of AF. However, the safety and efficacy of dronedarone has still not been proven following several recent studies. Additional studies in progress should help to identify the place in practice for this agent. Pharmacists should take great caution when using dronedarone in patients with NYHA class II, III and IV heart failure, as well as patients with permanent AF.

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Improving Maternal and Fetal Health: A Look at Thyroid Function During Pregnancy

Sarah Ginty, fourth-year pharmacy student from Olmsted Falls, Ohio; Jessica Beck, fourth-year pharmacy student from Gibsonburg, Ohio; Taylor Gauthier, fifth-year pharmacy student from Winnebago, Ill.; Amanda Meyer, fifth-year pharmacy student from Dublin, Ohio; Michelle Musser, PharmD, assistant professor of pharmacy practice

Abstract

Maintenance of thyroid function during pregnancy is critical for both maternal and fetal health and development; therefore, knowledge regarding the relationship between thyroid hormones and pregnancy is essential. The American Thyroid Association task force has developed clinical guidelines on the diagnosis and treatment of thyroid disease during pregnancy. Gestational thyroid diseases are divided into two classifications, hypothyroidism and hyperthyroidism, which are further divided into more specific classifications based on clinical presentation. Differentiation, diagnosis, and monitoring of thyroid diseases throughout pregnancy require assessing symptoms, as well as obtaining levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) concentration by a simple serum test. Treatment goals are based on trimester-specific normal ranges of these hormone levels. Uncontrolled hypothyroidism and hyperthyroidism during pregnancy can lead to adverse pregnancy complications and have negative effects on fetal development. However, debate still exists as to the benefit of thyroid hormone level screening in all pregnant patients versus only those with higher risk.

Introduction

Pregnancy has a significant impact on the thyroid gland and thyroid function. Knowledge regarding the relationship between thyroid hormones and pregnancy is advancing at a rapid pace.[1] Many studies are now focusing on the potential impact of hypothyroidism or hyperthyroidism, as well as treatment outcomes on maternal and fetal health. It is important to recognize that until between 10 and 12 weeks gestation, the fetus is entirely dependent upon placental transfer of maternal thyroid hormone. Although maintenance of maternal thyroid hormone levels is critical throughout the entire pregnancy, avoidance of suboptimal levels is of great importance during this time.[2] By the end of the first trimester, the fetal thyroid begins producing thyroid hormones on its own, but remains dependent on the mother for ingestion of adequate amounts of iodine, an essential component in the production of thyroid hormones. During pregnancy, the maternal thyroid gland increases in size by 10 to 40 percent. Along with a 50 percent increase in maternal daily iodine requirement, production of thyroxine (T_4) and triiodothyronine (T_3) also increases by 50 percent during this time. Serum thyroid-stimulating hormone (TSH) levels fall during the first trimester of a normal pregnancy as a physiological response to the stimulating effect of human chorionic gonadotropin (hCG) on the TSH receptor. Normal TSH levels during pregnancy range from 0.03 mIU/mL to 2.5 mIU/mL.[1]

The American Thyroid Association (ATA) task force has developed clinical guidelines for the diagnosis and treatment of thyroid disease during pregnancy. Hypothyroidism during gestation is defined as the presence of an elevated serum TSH concentration. Hypothyroidism is prevalent in 2 percent of pregnancies and can be further classified as either subclinical (SCH) or overt hypothyroidism (OH), dependent upon measurement of serum free thyroxine (FT_4) concentration. Hyperthyroidism is characterized by an overactive thyroid gland and defined by elevated FT_4, as a result of increased serum concentrations of T_4 and T_3, and suppressed or undetectable serum TSH.[1] Thyroid hormone fluctuations associated with hypothyroidism and hyperthyroidism have been shown to impact both maternal and fetal health and development.

Diagnosis and Complications of Hyperthyroidism During Pregnancy

Hyperthyroidism is less common during pregnancy than hypothyroidism. It is estimated that the prevalence falls in the range of 0.1 percent to 0.4 percent, with 85 percent of cases attributed to Graves' disease.[3] Graves' disease is most common in women during the reproductive years and can be associated with infertility. Most pregnant women with hyperthyroidism are diagnosed with Graves' disease prior to conception. In the first trimester, a diagnosis of Graves' disease is based on very low serum TSH (<0.1mIU/L) and elevated FT_4, which must be differentiated from gestational hyperthyroidism.[1] Gestational hyperthyroidism is characterized by low serum TSH and elevated FT_4 during the first half of pregnancy, as well as the absence of serum markers of thyroid autoimmunity. In patients with Graves' disease, TSH receptor antibodies (TRAb) will be present and physical findings may include a goiter or thyroid-associated orbitopathy. Obstetric complications, such as increased risk of stillbirth, miscarriage and premature birth, are similar to the complications seen with hypothyroidism.[3] Patients with uncontrolled hyperthyroidism during pregnancy may experience congestive heart failure, thyroid storm triggered by preeclampsia or maternal TRAb may cross the placenta and stimulate the fetal thyroid. Stimulation of the fetal thyroid can lead to fetal tachycardia, fetal growth retardation, cardiac failure, development of a fetal goiter and, rarely, neonatal hyperthyroidism.

Treatment and Monitoring of Hyperthyroidism

For patients with a diagnosis of Graves' disease, the safest time to conceive is while euthyroid.[1] It is strongly suggested that uncontrolled patients planning on becoming pregnant use adequate contraception until they become euthyroid. A hyperthyroid patient may be treated with ablative therapy or antithyroid drugs (ATD) prior to conception, but after con-

ception the preferred treatment is ATD. The main antithyroid drugs used are propylthiouracil (PTU) and methimazole (MMI).[3] During the first trimester, the current ATD of choice is PTU because more teratogenic effects have been associated with MMI.[1] Women on MMI prior to conception should be switched to treatment with PTU. After the first trimester, patients may consider switching to MMI because there have been reports of hepatotoxicity with prolonged PTU treatment.[1,3] Both PTU and MMI cross the placental barrier; for this reason, the lowest dose of ATD that maintains FT_4 levels at or moderately above the normal reference values should be used.[1] Levels of FT_4 and TSH should be monitored every two to six weeks during pregnancy with a primary goal of keeping FT_4 levels controlled. If maternal FT_4 levels are not under control, fetal heart rate, growth and thyroid size may be evaluated as needed using ultrasound.[4] Lactating mothers should be treated with MMI doses up to 30mg/day given in divided doses immediately following each feeding. PTU is typically avoided during lactation due the hepatotoxicity risks.[1]

Antithyroid drugs are not indicated for the treatment of gestational hyperthyroidism, because FT_4 levels return to normal by 14 to 18 weeks gestation.[1] Gestational hyperthyroidism may cause nausea and vomiting in the form of hyperemesis gravidum. Management should include supportive therapy for symptoms and hospitalization if required.

Diagnosis and Complications of Hypothyroidism During Pregnancy

Hypothyroidism can be difficult to diagnose during pregnancy.[5,6] Typical symptoms of hypothyroidism such as weight gain, muscle cramps, constipation, fatigue and dry skin are common symptoms of pregnancy itself. For this reason, a diagnosis of hypothyroidism is confirmed by an increase in serum TSH.[6] Hypothyroidism during pregnancy is differentiated into overt and subclinical types. The estimated prevalence of each type during pregnancy is 0.2 to 0.3 percent and 2 to 2.5 percent, respectively.[7] Overt hypothyroidism (OH) during pregnancy is defined as an elevated TSH level of greater than 2.5 mIU/L in conjunction with a decreased FT_4 concentration or a TSH level above 10mIU/L regardless of FT_4 levels.[1,8] Subclinical hypothyroidism (SCH) is defined as a TSH level within the range of 2.5mIU/L and 10mIU/L with a normal FT_4 level. OH is symptomatic whereas SCH may be symptomatic or asymptomatic.[5]

When left untreated, OH has been firmly associated with adverse pregnancy complications and negative effects on fetal brain development.[1,9] Depending on when during the pregnancy untreated OH is present, it can lead to infertility, increased risk of preeclampsia, premature birth, low birth weight, miscarriage, increased admission to neonatal intensive care and perinatal morbidity and mortality.[1,4,7] Maternal OH in all trimesters has been associated with the development of fetal neurological deficits, but during the third trimester the fetal thyroid gland is able to provide some thyroid hormone to the fetus lessening the severity of fetal brain damage occurring during the last trimester.[6,10] Untreated SCH is associated with similar adverse pregnancy outcomes, but whether or not it has negative effects on infertility or causes neurocognitive deficits in the developing fetus remains controversial.[1,10]

Treatment and Monitoring of Hypothyroidism

The goal of treatment for both OH and SCH is to normalize serum TSH to the following trimester-specific ranges: first trimester 0.1 mIU/L to 2.5 mIU/L; second trimester 0.2 mIU/L to 3.0 mIU/L; and third trimester 0.3 to 3.0 mIU/L .[1] It is important to note these ranges are lower than the 0.4 mIU/L to 4.0 mIU/L target range for non-pregnant women.[8] The American Thyroid Association recommends using levothyroxine (LT_4) thyroid preparations rather than T_3 or dessicated preparations.[1] Up to 50 to 80 percent of women receiving exogenous levothyroxine prior to pregnancy will require a dosage increase during pregnancy.[8] For patients planning a pregnancy and receiving exogenous levothyroxine for a diagnosis of hypothyroidism, a levothyroxine dosage adjustment should be made as soon as pregnancy is suspected or immediately after a missed menstrual cycle. The American Thyroid Association recommends an approximate 25 to 30 percent increase in dose for euthyroid newly pregnant women receiving levothyroxine.[1] This can be accomplished using a two tablet dosage increase based on a prospective, randomized trial by Yassa et al. The study demonstrated a reduced risk of maternal hypothyroidism during the first trimester when patients had their total weekly T_4 dose increased by two tablets.[11] For example, a woman on seven tablets per week would increase her dose to nine tablets per week.[1] Maternal TSH levels should be monitored every four weeks during the first 20 weeks of pregnancy for patients receiving levothyroxine and patients with untreated SCH because further dosage adjustments are often required to keep TSH in range. Maternal TSH should be checked again at least once between 26 and 32 weeks gestation. Thyroxine (T_4) requirements will likely increase as the pregnancy progresses.[6] Pharmacists can help maximize intestinal absorption of the hormone by counseling patients to take levothyroxine on an empty stomach with a glass of water, either one hour before or two hours after a meal and four hours apart from products containing iron such as prenatal vitamins.[6,12]

Postpartum, TSH levels and T_4 requirements should return to their pre-pregnancy state allowing patients to resume their pre-pregnancy dosing schedules.[1] TSH should be checked at six weeks postpartum.

Screening for Thyroid Function

There is much discussion as to the benefit of monitoring thyroid hormone levels during pregnancy, and it has been five years since the American Association of Clinical Endocrinologists recommended thyroid function screening in all women during the first trimester of pregnancy.[13] The most recent guidelines set forth by the Endocrine Society recommend screening in high-risk women as opposed to routine screenings in pregnancy.[14] High-risk women should be screened for thyroid function during and/or before pregnancy (Table 1).

Despite these criteria, a single-center cohort study that measured TSH, free T_4 and free T_3 in 1,560 consecutive preg-

nant women during their first visit to the gynecologist at a median of nine weeks gestation, discovered that thyroid function testing of only the high-risk women would miss about one-third of pregnant women with hypothyroidism (Table 1).[15] Thus, it is recommended from the results of this particular trial that all pregnant women receive thyroid function tests.

A 2008 study assessed the cost-effectiveness of screening for thyroid function during pregnancy by using a Markov model. Three strategies including no screening, screening with anti-thyroid peroxidase (TPO) antibodies and screening with TSH were evaluated in women with no known history of thyroid disease.[16] In the first screening, serum was tested for anti-TPO antibodies. If that was positive, the serum was tested for TSH. If TSH was high, FT_4 was tested. Treatment with levothyroxine was administered if necessary. Hypothyroidism costs were generated using the costs of a 10 minute follow-up visit, TSH test, FT_4 test, annual levothyroxine treatment, low IQ level, and gestational hypertension as opposed to no gestational hypertension. The study concluded that screening women with TSH in their first trimester saved $102 and increased maternal life expectancy by 5.84 days. Screening women with anti-TPO antibodies proved to be more cost-effective compared with TSH as maternal age increased. Thus, the cost of screening should not be a factor in determining whether all women should be tested for thyroid function during pregnancy.

Conclusion

Determining and treating thyroid function abnormalities during pregnancy is essential for the health of both the mother and the fetus. Simple serum tests can be done to test thyroid function, especially if the mother has a personal or family history of thyroid disease. Hypothyroidism can be confirmed by an elevated serum TSH level and, when left untreated, can be associated with adverse pregnancy complications and negative effects on fetal brain development. Levothyroxine can be used to treat hypothyroidism. Hyperthyroidism can be confirmed when serum TSH is very low and FT_4 is elevated. Patients with uncontrolled hyperthyroidism during pregnancy may experience maternal congestive heart failure, thyroid storm triggered by preeclampsia, or maternal TRAb may cross the placenta and stimulate the fetal thyroid leading to fetal tachycardia, growth retardation, cardiac failure, development of a fetal goiter, and rarely neonatal hyperthyroidism. Hyperthyroidism can be treated with antithyroid drug therapy, specifically propylthiouracil and methimazole. Although there is much debate as to whether or not thyroid function tests are necessary in pregnant women, studies show that testing is cost-effective and should be recommended to ensure the health of both mother and fetus.

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Table 1. Characteristics of Women at High Risk for Thyroid Disease[14]

Past history of thyroid disease	Goiter
Thyroid lobectomy	TRAbs
Family history of thyroid disease	Type I diabetes
Symptoms or clinical signs of hyperthyroidism	Symptoms or clinical signs of hypothyroidism
Autoimmune disorders	Infertility
Previous therapeutic head and neck irradiation	History of miscarriage and preterm delivery

Emerging Therapies for the Treatment of Multiple Sclerosis

Sara Swick, fourth-year pharmacy student from Pataskala, Ohio; Amy Gillman, fourth-year pharmacy student from Cincinnati, Ohio; Lauren Bajbus, fifth-year pharmacy student from Parma, Ohio; Jennifer Bauer, fifth-year pharmacy student from St. Marys, Pa.; Jeffery Talbot, Ph.D., assistant professor of pharmacology

Abstract

Multiple sclerosis is a neurological disease that affects millions of people worldwide, yet is not entirely understood. Symptoms of multiple sclerosis most frequently include muscle spasms and extreme fatigue, but patients can experience a wide variety of issues. There are four categories in which patients with multiple sclerosis are typically classified: relapse-remitting, primary-progressive, secondary-progressive and progressive-relapsing. The pathophysiology of the disease is largely unknown, but many theories are being researched. Currently, there are treatments that can alleviate symptoms and halt disease progression, but no cure is known at this time. Most symptomatic relief medications focus on anti-inflammatory mechanisms of action, while disease modifying treatments have novel mechanisms which are being studied more fully. By being aware of new drug therapies, pharmacists can better counsel patients with this disease state. As new therapies are approved, it is important to understand their mechanism and reasons for use, so as to be aware of potential side effects and interactions.

Introduction to Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory neurological disease that affects 2.1 million people worldwide including about 400,000 Americans.[1,2] An estimated 200 Americans are diagnosed with MS every week.[2] The hallmark of MS is a progressive autoimmune-mediated demyelination of neurons. The myelin sheath acts as an insulator, providing high resistance and low capacitance, resulting in greater impulse conduction velocity of neurons.[3] Thus, demyelination leads to slowed or blocked signal transmission. MS is characteristically idiopathic, in that a defined pathophysiology has not been determined. However, studies suggest a strong genetic influence, as first-degree relatives of an affected individual are 20 times more likely to be diagnosed with MS than the general population. In addition, case studies have found that patients with MS have elevated levels of antibodies targeting Epstein-Barr virus proteins, suggesting the virus may initiate inflammatory responses that lead to autoimmune demyelination, characteristic of MS.[4-6] The onset of symptoms and diagnosis typically occurs between the ages of 20 and 50; women are two to three times more likely to be affected by MS than men.

Symptoms

The symptoms of MS are common to many neurologic disorders and are erratic, affecting the muscles, bowel, bladder, eyes, brain and spine.[6] The most frequent symptoms associated with MS are fatigue and muscle spasticity. However, affected individuals may also experience muscle stiffness, disequilibrium, paralysis of the limbs and bowel, mood and behavioral changes such as depression, impaired vision, slurred speech and incontinence. Symptoms range in intensity from mild to severe, with high inter-patient variability. The degree of discomfort and disability associated with MS depends on the frequency and severity of attacks, and the area of the nervous system affected. MS is typically identified by differential diagnosis due to high variability in patient presentation and symptom commonality with other neurologic disorders.[2]

Effective management of symptoms improves quality of life and is imperative to prevent permanent damage that can result in disease progression and worsening symptoms.[1] Pharmacological treatments may include corticosteroids to decrease inflammation in nervous tissue and reduce the duration and severity of flare-ups. Muscle relaxants, such as tizanidine (Zanaflex®) or baclofen (Lioresel®), reduce stiffness and muscle spasticity. Plasma exchange may also be used for patients who do not benefit from corticosteroid therapy and experience sudden, severe attacks of MS-related disability. The antiviral drug amantadine (Symmetrel®) or the stimulant modafinil (Provigil®) may be used for fatigue-like symptoms. An anticholinergic medication such as tolterodine (Detrol®) may be used for incontinence by blocking contractions of the bladder.[6] Since mood and behavioral symptoms are also common, antidepressants can be used in MS patients, while non-pharmacological approaches such as physical, speech or occupational therapy may help maintain independence in activities of daily living. Individual or group therapy can help with the emotional stress of coping with the disease. Assistive devices such as a wheelchair, walker or shower chair, as well as a healthy lifestyle and planned exercise program, have also been noted to help with some of the movement issues a patient will experience. As with many diseases, avoiding illness, stress and fatigue with plenty of relaxation and rest can improve symptoms.

Clinical Classification of Multiple Sclerosis

Multiple sclerosis can be loosely classified into one of four clinical categories: relapse-remitting, primary-progressive, secondary-progressive and progressive-relapsing.[7] The following descriptions are used for the four categories:

Relapse-Remitting MS (RRMS): Patients experience bouts of worsening neurologic function known as relapses. These flare-ups last anywhere from a few days to months and are contrasted by periods of remission characterized by full or partial recovery, during which no disease progression occurs. The flare-ups must last at least 24 hours and be separated from the previous attack by at least one month. No two flare-ups are alike. They may include just one symptom or involve multiple symptoms. Most patients are initially diagnosed in this category but many will progress to secondary-progressive MS.

Primary-Progressive MS (PPMS): The hallmark of PPMS is a worsening neurologic function from disease onset, without a clear pattern of relapse and remission.

Secondary-Progressive MS (SPMS): This classification is an example of the blurred boundaries between classifications because it is difficult to clearly distinguish it from PPMS due to their similarities. It is characterized as worsening of neurological function, with more irreversible damage occurring, with or without flare-ups and minor relapses. Thus, over time, symptoms associated with relapse become worse, while remissions are less prominent and shorter in duration, eventually becoming non-existent.

Progressive-Relapsing MS (PRMS): This classification is relatively rare. Patients experience a steady worsening of the disease from the beginning without remissions. Patients may experience clearly-defined relapses that may slow after some time; however, the disease is always continuing to progress.

Pharmacotherapy

Currently no cure for MS exists; however, treatment options are available for patients based on an anti-inflammatory strategy to slow disease progression.[1,2] First-line treatments are intramuscular or subcutaneous interferon β (Rebif®) and subcutaneous glatiramer acetate (Copaxone®), both of which are indicated for RRMS. The exact mechanism of action of interferon β is unknown. However, it has been proposed to suppress the T-helper cell response, thereby diminishing T-cell migration across the blood-brain barrier, which reduces the inflammatory process. Common adverse effects consist of flu-like symptoms, depression and elevated hepatic enzymes. The mechanism of action of glatiramer acetate is not fully understood, but is thought to involve alteration of T-cell activation and differentiation. Common adverse effects are similar to those seen with interferon β, including injection-site reactions and depression, as well as lipoatrophy. These two drugs should be avoided in patients with a coexisting depressive disorder. The BEYOND, BECOME and REGARD trials compared the two first-line agents and found them to have comparable efficacy, with no significant differences regarding relapse rate, disability progression or magnetic resonance imaging (MRI) outcomes.[1,8,9]

Second-line agents are intravenous mitoxantrone (Novantrone®) and intravenous natalizumab (Tysabri®).[2] Mitoxantrone was the first approved disease-modifying therapy indicated for multiple MS classifications (RRMS, SPMS, PRMS).[1,2] Mitoxantrone works by intercalating DNA and inhibiting topoisomerase II. This results in DNA breaks and inhibition of DNA repair, causing reduced proliferation of B- and T-cells and reduced release of inflammatory cytokines. This agent is associated with rare but serious side effects of cardiotoxicity and severe bone marrow suppression, thus it is not considered a first-line agent. More common adverse effects associated with treatment include nausea, vomiting, alopecia and leukopenia. Mitoxantrone is used when patients progress from RRMS to a more severe stage of MS. The other second-line agent, natalizumab, is a humanized monoclonal antibody that inhibits leukocytes from crossing the blood-brain barrier by antagonizing a4 integrins on leukocytes.[1] This monoclonal is not a first-line agent due to its association with progressive multifocal leukoencephalopathy (PML), a potentially fatal infection caused by the JC polyomavirus. The more common adverse events are headache, fatigue, allergic reaction and infection. These two treatments are reserved for patients who cannot tolerate or are unresponsive to first-line agents.

Emerging Therapies: FDA Approved

Two new agents were approved by the Food and Drug Administration (FDA) in 2010 for the treatment of MS, both with novel mechanisms relative to existing therapies—dalfampridine (Ampyra®) and fingolimod (Gilenya®).[3] Dalfampridine is the only FDA approved symptom management treatment to improve walking in all types of MS. Although there is disagreement on the exact mechanism by which dalfampridine exerts its therapeutic effects, it is classified as a voltage-dependent potassium channel blocker that lowers the seizure threshold. Studies showed efficacy in one-third of patients and the most common adverse effects were falls, urinary tract infections, insomnia, asthenia, headache, nausea and dizziness.

The second medication, fingolimod, is considered a disease-modifying treatment, and is a sphingosine 1-phosphate receptor modulator. In vivo, fingolimod is a prodrug which has a phosphorylated active metabolite that exerts its therapeutic effects by decreasing the release of autoreactive lymphocytes. This lowers the amount of peripheral lymphocytes and sequesters lymphocytes in the lymph nodes.[10] There is also potential for neuroprotective and/or reparative functions.[11] Importantly, with this novel mechanism, it is the first FDA approved oral treatment for relapsing forms of MS and is now considered first-line treatment for RRMS.[1,10] Fingolimod is metabolized by CYP4F2; however, drug-drug interactions are not likely because other drugs currently on the market are not metabolized by this enzyme.[10] The most common adverse effects experienced were headache, influenza, diarrhea, back pain, liver enzyme elevations and cough. Serious adverse events of bradycardia, MS relapse, basal cell carcinoma and chest pain occurred in less than 1 percent of patients. Recent reports of patient deaths after taking the first dose of fingolimod have also led to label changes guiding practitioners in appropriate patient populations. The updated FDA label for Gilenya® indicates that all patients initiating treatment with Gilenya® should have an electrocardiogram (ECG) prior to the first dose of the medicine and after the six-hour first-dose observation period in addition to hourly measurement of blood pressure and heart rate.[12] Additionally, specific initiation guidance for patients is now provided to better aid health care providers. Further, there are revised recommendations on how to re-initiate therapy should Gilenya® be interrupted.

Emerging Therapies: New Labeling in Clinical Trials

In addition, several medications are under investigation for new labeling in the treatment of MS that are currently approved for different indications. These are cladribine (Leustatin®) and the monoclonal antibodies alemtuzamab

(Campath®), daclizumab (Zenapax®) and rituximab (Rituxan®). Cladribine was approved in 1993 for the treatment of hairy cell leukemia.[13] Currently a variety of studies exist evaluating the use of cladribine in treatment of MS as an add-on to interferon β or an oral formulation.[14] Cladribine is hypothesized to exert its effects as an immunomodulatory purine analog with lymphocytotoxic activity. This would act by damaging DNA and thereby cause selective cell death of lymphocytes.[2] It is generally well-tolerated, with adverse effects of headache, nasopharyngitis, upper respiratory tract infection, urinary tract infection, alopecia and sensory disturbances. Monoclonal antibodies exert their effects by recognizing specific target antigens ultimately resulting in differing immunosuppressive mechanisms. Alemtuzumab and daclizumab are both humanized monoclonal antibodies that are slightly less immunogenic due to only one small non-human portion in the complement sequence. Alemtuzumab reduces the number of circulating T-cells, while daclizumab antagonizes IL-2 on activated lymphocytes, which is responsible for the up-regulation of the immune system. Rituximab is a chimeric monoclonal antibody causing more immunogenic reactions due to the presence of the murine antigen-binding domain. It exerts its effects by selectively depleting CD20 pre-B-cells and B-cells ultimately causing cytotoxicity. The major concern with monoclonal antibodies would be the adverse effect profile requiring careful monitoring of their use with other immunosuppressant medications. This concomitant use may cause depletion of multiple cell lines, which could lead to potentially serious infections. Adverse effects associated with these monoclonal antibodies are systemic immune responses such as mouth ulcers, photosensitivity rash, transient formation of autoantibodies, lymphopenia, lymphadenopathy and transient increases in bilirubin concentration.

Emerging Therapies: Orphans in Clinical Trials

Three immunomodulator medications are currently in clinical trials for new MS treatments: laquinimod, teriflunomide and dimethyl fumarate.[2] The mechanism of action of laquinimod has not been fully defined, but is proposed to work via immunomodulatory properties with potential neuroprotection.[15] Infiltration of leukocytes into the central nervous system (CNS) leads to destruction of white matter and neurological impairment. It is hypothesized that laquinimod acts by reducing demyelination and axonal degeneration via changes in the cytokine shift. Studies have shown laquinimod to be generally well-tolerated, with minimal differences between the placebo and laquinimod groups regarding adverse effects.[2] Teriflunomide exerts its effects via anti-inflammatory and antiproliferative properties.[15] Teriflunomide is the active metabolite of leflunomide, a commonly used treatment in rheumatoid arthritis. Thus far, it has exhibited a favorable safety profile and efficacy in the treatment of aspects of rheumatoid arthritis that are similar to the autoimmune reaction in MS patients. Teriflunomide exerts its effects by decreasing activation of T-cells by antigen presenting cells.[2] Dimethyl fumarate is an orally administered immunomodulatory agent that inhibits microglia and astrocytes via the Nrf2 signaling pathway, resulting in reduced CNS inflammation.[1] The most common side effects were abdominal pain and flushing (Table 1).

Pharmacist's Role

With approximately 400,000 Americans diagnosed with MS, pharmacists play a critical role in improving patient outcomes. Continued development of an increasing number of novel treatment modalities make it imperative for pharmacists to be informed on the current therapies. In addition, with the recent approval of oral medications to treat MS, the

Table 1. Potential Indications for Emerging MS Therapies[2]

Drug	RRMS	SPMS	PPMS
Fingolimod	+	+	NR
Laquinimod	+	+	NR
Teriflunomide	+	+	NR
Dimethyl Fumarate	+	NR	NR
Cladribine	NR	+	+
Alemtuzumab	+	NR	NR
Daclizumab	+	+	NR
Rituximab	+	NR	+

NR= not reported
Adapted from Gawronski, et al. Table 3 p 921.

role of the pharmacist is no longer limited to inpatient clinical monitoring and counseling but has expanded to include the outpatient setting. Thus, it is increasingly likely pharmacists will be needed for the education of patients as well as other health care professionals on current and emerging treatments for MS.

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The Impact of Pharmacogenomics on Chemotherapeutic Drug Development and Use

Lara Long, fourth-year pharmacy student from Terre Haute, Ind.; Amy Pasternak, fourth-year pharmacy student from Akron, Ohio; Ellen Hazelet, fifth-year pharmacy student from Columbia City, Ind.; David Kisor, BS, PharmD, professor of pharmacokinetics, chair of the department of pharmaceutical and biomedical sciences

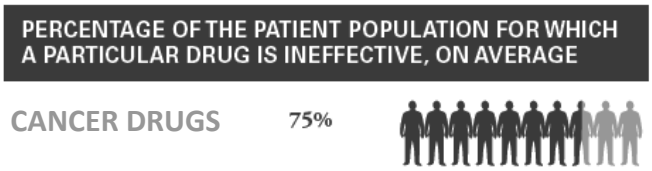
Abstract

Cancer therapy is largely dependent on general treatment guidelines, and patients undergoing chemotherapy often experience treatment failure with standard drugs. The development of individualized drug therapy through pharmacogenomics has the potential to enhance chemotherapy regimen selection and improve patient outcomes. Antineoplastic agents such as cetuximab and trastuzumab are effective in treating cancers possessing specific genetic biomarker characteristics. Patients need to undergo genetic testing before these agents are administered to ensure appropriate use. Cetuximab has been shown to improve outcomes in metastatic colorectal cancers and head and neck squamous cell carcinomas positive for EGFR. Trastuzumab has shown benefit in human epidermal growth factor receptor 2 (HER2) overexpressing cancers affecting the breast tissue and gastrointestinal tract. High costs associated with the development of targeted drugs and a lack of clinical studies exploring the effects genetic variations can have on drug therapy limit implementation of pharmacogenomics into routine practice. As drug therapy experts, pharmacists need to be aware of advances in the field of pharmacogenomics and facilitate the use of this new class of personalized drugs.

Introduction

Patients diagnosed with cancer are treated on the basis of standard drug therapy and dosing guidelines.[1] Many factors, such as body weight, age and medical history, may also be considered in choosing a medication regimen. Despite these considerations, a patient's response to drug therapy cannot be predicted using current methods and practice guidelines. This could translate into repeat visits to the oncologist for medication changes and additional rounds of chemotherapy, with an increased risk of incapacitating side effects. For patients diagnosed with cancer, therapeutic failure can be devastating and there is often little time for a trial and error approach. The development of individualized therapy through pharmacogenomics has the potential to enhance chemotherapy regimen selection and improve patient outcomes. Targeted antineoplastic medications, such as cetuximab and trastuzumab, can be extremely beneficial in oncology patients with specific genetic variant biomarkers, but also have the potential to cause life-threatening adverse effects. In order to reduce patients' exposure to dangerous medications in the absence of a potential benefit, genetic testing is required prior to administration of these drugs to identify those patients who will most likely exhibit a positive response. Despite the obvious benefits of pharmacogenomics, barriers exist in both research and integration into practice. Pharmacists are in a key position to advocate for individualized drug therapy and to inform other health care providers on the use and benefits of pharmacogenomics.

Figure 1. Average chemotherapeutic drug failure.[2]



Cetuximab

Cetuximab (Erbitux®) is a recombinant chimeric IgG_1 antibody that binds to the extracellular domain of epidermal growth factor receptor (EGFR)-1. EGFR is responsible for the growth and differentiation of epithelial cells. When epidermal growth factor (EGF) binds to the extracellular domain of EGFR, receptor dimerization occurs and intracellular protein tyrosine kinases are activated. Following kinase activation, various signaling pathways are stimulated, such as RAS-RAF-mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K-AKT) pathways. Once activated, these pathways' signals can regulate cell proliferation, differentiation and survival. Cetuximab binds to the extracellular domain of EGFR with high affinity and competitively inhibits ligands from binding to the receptor.[3] This leads to inhibition of phosphorylation of intracellular protein tyrosine kinases and prevents the activation of the downstream signaling pathways, resulting in the inhibition of cell growth and proliferation, ultimately inhibiting tumor growth (Figure 2).

Cetuximab was the first EGFR inhibitor approved for the treatment of metastatic colorectal cancer (mCRC). It is used as monotherapy in the treatment of EGFR-positive mCRC in patients who cannot tolerate traditional irinotecan-based therapy or in combination with irinotecan in patients who did not respond to oxaliplatin, irinotecan and 5-fluorouracil (5-FU). Traditional therapy in the treatment of mCRC includes a combination of 5-FU or capecitabine, with either oxaliplatin or irinotecan. Using cetuximab in combination with 5-FU and irinotecan or oxaliplatin has been shown to improve outcomes in the first- and second-line setting of mCRC.

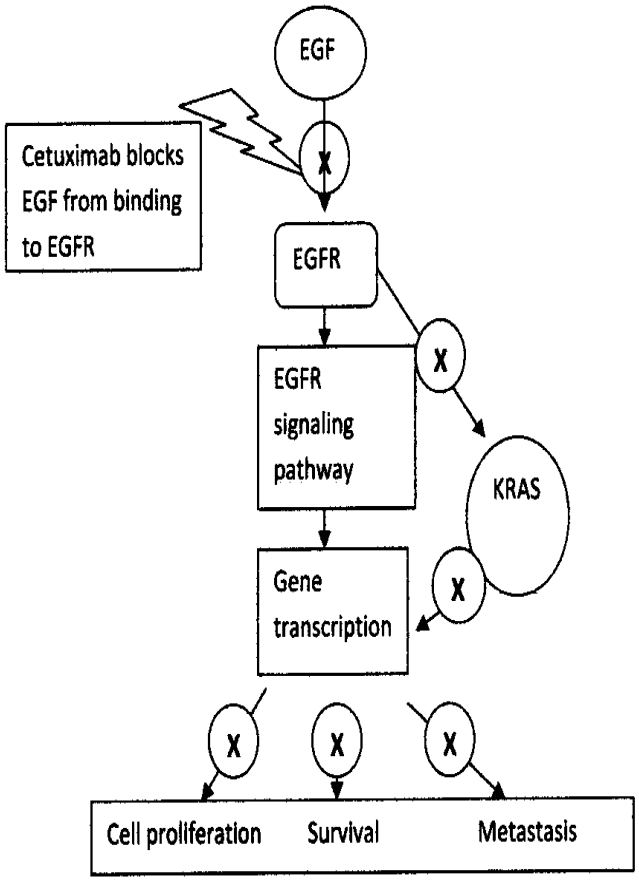
Cetuximab can improve overall survival when used in combination with radiation therapy in the treatment of locally or regionally advanced head and neck squamous cell carcinoma (HNSCC). It is used as a monotherapy agent in patients with metastatic or recurrent HNSCC. These patients do not typically respond to platinum-based chemotherapy. Cetuximab

has also been shown to improve survival when used in combination with cisplatin-based chemotherapy, as compared to cisplatin alone.[4]

KRAS Mutation

RAS proteins are involved in the EGFR signaling pathways that ultimately result in cell proliferation, differentiation and survival. The three human RAS genes—HRAS, KRAS and NRAS -- are involved in the pathogenesis of tumors through cell proliferation, angiogenesis and anti-apoptosis pathways.[3] RAS proteins are small GTP-GDP-binding proteins which act as self-inactivating signal transducers cycling from the GDP- to GTP-bound states as a result of EGF binding to the EGFR. These oncogenic RAS proteins have reduced GTPase activity which results in an abundance of RAS proteins in the GTP-bound active state due to an inability to cycle back to the GDP -bound inactive state. This results in further activation of the downstream signaling pathways promoting cancer cell proliferation, angiogenesis and resistance to apoptosis. Mutations in the coding region of the KRAS gene lead to a constitutively active gene, which is not dependent on upstream activation of the EGFR. Cetuximab prevents the downstream cell signaling pathways from occurring by blocking EGF from binding the EGFR. Because EGFR activation results in KRAS protein activation, mutations in the coding region of the KRAS gene lead to a constitutively active KRAS gene. This mutated KRAS gene is not dependent on the upstream signaling pathways.[5]

Figure 2: Cetuximab and its effects on the EGF pathway.[3]



A randomized trial completed by the National Cancer Institute of Canada Clinical Trials Group with the Australasian Gastro-Intestinal Trials Group demonstrated that patients harboring KRAS mutations had reduced response rates to cetuximab therapy, compared to patients with wild-type KRAS genes. The cetuximab therapy group revealed that patients with wild-type KRAS tumors had a response rate to cetuximab that was 12.8 percent, compared to a 1.2 percent response rate in patients with a mutated KRAS gene.[6]

Mutations of the KRAS gene occur as point mutations in codons 12 and 13 of exon 2. These mutations occur early in the development of mCRC carcinogenesis. Thirty-five to 40 percent of colorectal cancer (CRC) cases have KRAS mutations. KRAS mutation incidence is identical among all stages of CRC. Identification of KRAS mutations are considered to be a predictor of testing resistance to anti-EGFR monoclonal antibody therapy.[3] The American Society of Clinical Oncology Provisional Clinical Option has issued a recommendation that all patients with mCRC that are candidates for anti-EGFR monoclonal antibody therapy must have tumor cells tested for the presence of KRAS mutations prior to initiating drug therapy.[7] If the results show a KRAS mutation in codons 12 or 13, patients should not receive anti-EGFR monoclonal antibody therapy due to predicted resistance.

Testing for KRAS Mutations

KRAS mutations are detected by the DxS-K-ras test kit. It can detect seven somatic mutations on codons 12 and 13 on the KRAS gene. The kit has seven primers that are specific in detecting the most common mutations in codons 12 and 13. These primers are complementary to the KRAS gene immediately adjacent to the mutation sites. Each primer has a unique sequence at the 3' end specific for the mutation. During polymerase chain reaction (PCR) amplification, the primers attach to the template strand and only the primer with the complementary nucleotide at the 3' end will extend the mutated target DNA.[5] Taq DNA polymerase is used in this test because it is very effective in distinguishing the differences between a match and mismatch nucleotide at the 3' end of a PCR primer. If the primer completely matches, amplification will occur with full efficiency; in the case of a 3' nucleotide base pair mismatch, amplification is reduced. This means only the mutated strand that matches the primer will be able to be extended. Amplification is detected using Scorpions, which are bifunctional molecules with a PCR primer covalently linked to a fluorescent probe. The fluorophore in the probe reacts with a quencher in the probe which results in a reduction in fluorescence. During the PCR amplification the probe binds to an amplicon, causing the fluorephore and quencher in the probe to become separated and increasing the amount of fluorescence observed in the reaction tube. Mutated KRAS genes will demonstrate a greater fluorescence reaction than wild-type KRAS genes because the mutated genes have a greater amount of amplification during PCR than the wild-type KRAS gene.[8]

Alternative Treatment Options for Patients with KRAS Mutations

The KRAS oncogene is the most commonly mutated gene in different human cancers and, due to its constitutive activity, it has the ability to bypass EGFR signaling cascade, therefore conferring resistance to anti-EGFR therapies such as cetuximab. Since patients with mCRC harboring KRAS mutations do not show a clinical response to cetuximab, they will have to consider other treatment options in order to control and treat their cancer. Some of these options include therapy that targets molecules downstream of RAS proteins such as RAF inhibitors. RAF is an effector molecule downstream of RAS in the ERK signaling pathway, making it a potential target for treating KRAS mutated tumors. Sorafenib, one of the first RAF inhibitors, has multikinase inhibitory actions against CRAF, BRAF, V600E mutant form of BRAF, vascular endothelial growth factor receptor (VEGFR) and platelet derived growth-factor receptor (PDGFR). Sorafenib has been approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma; however it is a relatively weak RAF inhibitor. Another option is using a combination of targeted agents. Since RAS activation results in activation of various branching pathways, blocking one downstream target of RAS will theoretically not be enough to inhibit tumor growth. Dual-targeted or multi-targeted therapy may be more efficient in eliminating cancer cells and fighting drug resistance in those patients with KRAS mutations.[3]

Trastuzumab

Trastuzumab (Herceptin®) is a human epidermal growth factor receptor 2 (HER2) antagonist. It is indicated as a treatment option in HER2 overexpressing cancers such as breast cancer in combination with doxorubicin, cyclophosphamide and paclitaxel or docetaxel; metastatic breast cancer as an adjuvant treatment with paclitaxel or used alone; and metastatic gastric or gastroesophageal junction adenocarcinoma in conjunction with cisplatin, capecitabine or 5-FU.[9]

Epidermal growth factor receptors (HER) dimerize upon ligand binding, thereby activating the receptor's tyrosine kinase activity. There are four types of HER proteins: HER1, HER2, HER3 and HER4. HER2 has no endogenous epidermal growth factor ligand, but has been determined to be the most preferential binding partner for dimerization with HER1, HER3 and HER4 and therefore acts primarily as a co-receptor.[10] These heterodimeric receptors have altered phosphorylation sites and cause modified activity. The HER2 heterodimers decrease the internalization of the receptor thereby amplifying and diversifying the altered signaling pathways. These signals ultimately lead to the formation of cancer through increased cellular proliferation and, potentially, metastasis of these cancers by increasing the cellular migration. It has been observed that HER2 is immunogenic, as many cancer patients express cytotoxic T-lymphocytes (CTL) which target HER2.[11] Trastuzumab inhibits this cellular proliferation and migration by binding to HER2 and inducing antibody dependent cellular cytotoxicity (ADCC). It also causes an upregulation of the MHC-class 1 receptors containing the HER2 epitope in overexpressing cancer cells.[11] Trastuzumab is only efficacious in HER2 overexpressing cancers, which is why genetic testing must be performed before it can be prescribed. The most recent indication for this medication is in esophageal adenocarcinoma (EAC). Two different EAC cell lines, OE19 and OE33, both overexpress HER2. Researchers compared trastuzumab efficacy in these cell lines and a non-HER2 overexpressing cell line. Both the OE19 and OE33 cell lines had inhibited proliferation when treated with trastuzumab, while the non-HER2 overexpressing cell line had no alteration in cellular growth when treated with trastuzumab. Levels of interferon-*y* (INF-*y*) produced by the OE33 cell line were significantly greater when treated with trastuzumab resulting in an increased cytotoxicity to the cell line. The OE19 cell line did not initially have the increased cytotoxicity associated with trastuzumab administration, owing to a deficiency of the TAP-2 protein, an antigen peptide transporter. The TAP-2 protein is required for proper antigen processing by the MHC-class 1 molecules. However, when treated with INF-*y*, an upregulator for the TAP-2 protein and then treated with trastuzumab, the OE19 cell line was also sensitized to cytotoxicity by CTLs through a MHC-class 1 mediated process.[11]

The HER2 proto-oncogene is found on the long arm of chromosome 17. Determination of HER2 protein and gene overexpression is performed through immunohistochemisty (IHC) and *in situ* hybridization, either fluorescence (FISH) or chromogenic (CISH), respectively.[12] IHC determines a positive or negative result for HER2 overexpression through the percentage of membrane staining that occurs; if over 30 percent of the cells in the sample have complete membrane staining, a +3 or positive score is assigned.[13] A FISH result is determined by the ratio of the number HER2 signals to the number of chromosome 17 signals; the result is considered positive for HER2 overexpression if the ratio is greater than 6 to 1.[13] However, the American Society of Clinical Oncology (ASCO) reports that approximately 20 percent of all testing may be inaccurate.

The limitations to determining HER2 overexpression in cancer are due to a variety of factors. The IHC scoring interpretation can be highly variable among different laboratories. In order to minimize this subjectivity, recent studies have used both IHC and FISH to properly determine HER2 expression. In a 2011 study all +3 IHC results also had HER2 amplification.[12] The limitation of the FISH ratio is due to the potential of chromosome 17 variations in the centromere. The centromere can exhibit polysomy, having too many copies of the centromere or monosomy, having only one copy of the centromere and these alterations are thought to contribute to the inaccuracy of testing.[14] This study demonstrated that artificial skewing due to an altered centromere caused false positive or false negative results. In the case of monosomy, positive results should be considered with caution as the decreased centromere number can produce an overexaggerated HER2/CEP17 ratio. In cases of polysomy, negative results should be closely examined as a lower than expected ratio may occur if the CEP17 has many more than two centromeres.[14] These factors must therefore be taken into careful consideration when conducting the mandatory genetic

testing prior to prescribing trastuzumab.

Motivations and Limitations to Pharmacogenomic Drug Development

Although pharmacogenetic testing has not become commonplace in all pharmaceutical settings, it is becoming increasingly prevalent before prescribing and to determine dosing for many oncology treatments. Many different types of cancer can now be identified based upon the specific genetic factors present. Cancer treatments are now being tailored to target these specific mutations, allowing these treatments to be more specific and efficacious. All chemotherapeutics have the potential for life-threatening adverse effects and should therefore not be prescribed unless the potential benefits outweigh the risks, a determination which cannot be conclusively made for some drugs without the use of genetic testing.

The limitation to this testing and development of genetically targeted drugs lies within the fact that the current costs to develop these medications do not cover the potential financial gains from these developments. Although the financial gains may not meet the costs of development, the quality of life (QOL) improvements gained by patients from these medications justify continued research. A 2008 study in Sweden demonstrated that the costs of FISH testing and concurrent treatment with trastuzumab for positive results (cost approximately $63,000) provided a gain of almost 1.5 quality adjusted life years (QALY). The average costs of these treatments were below the typical willingness to pay threshold and therefore this treatment regimen is superior to chemotherapy without FISH testing, which provided a lower QALY improvement.[15] Another limitation to the implementation of more frequent genetic testing is the lack of pharmaceutical studies currently conducted on the effects of genetic variation on drug metabolism and overall effect. This kind of research would allow for the research and development of more targeted medications and could also potentially decrease the frequency of adverse events and toxicity by ensuring chemotherapeutics or other drug agents are only used within populations which will see benefits outweighing the risks associated with the drug treatment course.

Conclusion

The benefits of pharmacogenomics have already been observed in chemotherapy through the cases of cetuximab and trastuzumab. Both agents have demonstrated effectiveness in oncology patients possessing specific genetic biomarker characteristics. Cetuximab has been shown to improve outcomes in metastatic colorectal cancers as well as head and neck squamous cell carcinomas positive for EGFR. Trastuzumab has shown benefit in HER2 overexpressing cancers affecting the breast tissue and gastrointestinal tract. Utilizing genetic testing is essential for appropriate use of these drugs. Personalized treatments can greatly improve chances of survival through earlier administration of effective drug therapy and decreased exposure to toxic antineoplastic agents unlikely to provide benefit to the patient.[16] Developing clinical pharmacy services in pharmacogenomics is one possible step in implementing the routine use of personalized drug therapy. Pharmacy services could include providing guidelines to physicians regarding genetic testing, initial drug selection and dosage adjustments.[17] Although pharmacogenomics is still in the early stages in practice, pharmacists can play a vital role in the implementation and use of pharmacogenomics in therapeutic decision making.

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E-Prescribing: Benefits and Challenges in Enhancing Patient Safety

Kayla Durkin, fourth-year pharmacy student from Valencia, Pa.; Rebecca Airel, fourth-year pharmacy student from Strongsville, Ohio; Lauren Desko, fifth-year pharmacy student from Perrysburg, Ohio; Jamie Amero, fifth-year pharmacy student from Boardman, Ohio; **Natalie DiPietro**, PharmD '01, MPH, assistant professor of pharmacy practice

Abstract
As technology is becoming ever more prevalent in the delivery of health care, implementation of electronic prescribing (e-prescribing) has proven to be beneficial in many aspects. However, new challenges have arisen which may be problematic for pharmacy workflow and patient safety. Pharmacists must recognize potential medical errors due to e-prescribing and take the lead on identifying and preventing such errors to enhance patient safety.

Introduction

According to The Institute of Medicine (IOM) report "To Err is Human," at least 44,000 people and as many as 98,000 people die in hospitals each year due to medical errors which could have been prevented.[1] In "To Err is Human," medical errors are defined as "the failure of a planned action to be completed as intended, or the use of a wrong plan to achieve an aim."[1] Adverse drug reactions (ADRs), which can be caused by medical errors, are defined by the World Health Organization (WHO) as "harmful, unintended reactions to medicines that occur at doses normally used for treatment." According to the WHO, "ADRs are among the leading causes of death in many countries."[2] Prevention of these events is critical for patient safety. In addition, prevention could save billions of dollars for the health care system. Total costs from medical errors have been estimated between 17 and 29 billion dollars each year.[1] There are many strategies for improvement and it will take time and effort to see a change in rates of medical errors in our current health care system.

An area emerging as a strategy to decrease medication errors and improve continuity of care is health information technology (HIT). The U.S. Department of Health and Human Resources defines HIT as "the use and exchange of health information in an electronic environment."[3] The use of HIT allows information to be accessed quickly and to be shared in order to enhance patient care.[4] Integrated HIT can allow health care providers to improve the completeness of patient information as well as better coordinate care. "Facilitating the meaningful use of HIT and exchange of health information among health care and public health professionals" are among the goals of Healthy People 2020, an initiative designed to improve the nation's health.[5] HIT can positively impact patient health and the U.S. health care system in many ways, one of which includes decreasing medical errors. One component of HIT that may reduce medical errors is the use of electronic prescribing (e-prescribing).

E-prescriptions are prescriptions created by a health care provider that are sent electronically through a private, secure and closed network to a pharmacy.[6] Since the prescription is sent directly from the physician to the pharmacy electronically, it is thought that this will decrease the amount of errors that arise from handling the prescription. To make this process as secure as possible, the equipment used for e-prescribing must be certified to perform these tasks of proper transmission. E-prescribing is seen as a great opportunity to improve the health system and incentives are being given to physicians to help transition to a more uniform health care system.[7] Adoption of the e-prescribing system has grown rapidly over the past few years. The National Progress Report on E-prescribing and Interoperable Healthcare found that in 2004, only 0.4 percent of office based prescribers used e-prescribing, but by 2007, e-prescribing became legal in all 50 states.[8] In that same year, the National E-Prescribing Safety Initiative was launched to help prescribers use e-prescribing properly to avoid medication errors.[8] The progress report also found that prescriptions routed electronically grew 72 percent from 191 million in 2009 to 326 million in 2010.[8] Although these numbers are impressive and e-prescribing may help decrease errors, more needs to be done to assess its efficacy. While HIT can lead to better patient safety, it can also introduce new risks.[9] Gaps in implementation make it hard to examine its beneficial impact.[9]

Documented Benefits and Challenges With E-prescribing

E-prescribing streamlines daily pharmacy practice and prescriber/pharmacy interaction in a technologically advanced society. The director of the Agency of Healthcare Research and Quality, Carolyn Clancy, MD, has said "the handoff of prescription data is at the heart of e-prescribing's potential to save time and advance patient safety."[10]

E-prescribing systems have been shown to be a key resource in recognizing and decreasing the number of prescription errors.[11,12] This mode of prescribing eliminates the need for handwriting interpretation, mitigating pharmacists' need for clarification.[11,12] E-prescribing may also decrease errors by providing decision support for the clinician.[11] Prescribers save time when using e-prescribing, especially for renewal prescriptions.[12] Electronic transmission also simplifies workflow for pharmacy staff by reduction in manual entry and minimization of interruptions such as phone calls and fax transmissions, further decreasing error rates.[12]

Providers and pharmacies are using electronic health records and e-prescribing for many reasons, including the reduction of medication errors. However, complications in the current system hinder some of the apparent benefits and may cause much frustration to pharmacists. Implemented applications should be reviewed and adjusted as needed.

For example, one commonly reported problem is with transmission of prescriptions; this problem is currently often reported when transmitting the prescription to a mail order pharmacy.[13] In addition, some community pharmacies have reported that the patient may arrive before the prescription has actually been received or processed. Pharmacies have also stated that electronic renewals were not as easy to integrate into the system as new prescriptions.[12] Another current issue with e-prescribing software programs is "over-specification" where prescribers must select certain attributes such as quantities or dosage forms; this is a challenge for certain medications such as prepackaged or multi-use medications.[12] Also, e-prescribing systems require periodic maintenance and crashes are seen as common occurrences.[13]

Some studies have found the rate of errors with e-prescribing to be comparable to those of written prescriptions.[14] One study found that omission of key information was the most common error. This includes proper doses or how long/how many times a day a medication should be taken. Improper abbreviations, conflicting information about how or when to take the drug and clinical errors in the choice or use of the treatment were also errors found.[14] Some of the errors documented are unique to e-prescribing. Computer-related errors can include inadvertent ordering of duplicate medications; selecting an unintended medication from a drop-down menu; and errors in keypad entry/ typographical errors.[15] Errors can be also be generated by fragmentation of information between multiple computer screens, lack of integrated computer systems and implementation of processes that do not correspond to workflow.[13]

The Pharmacist's Role in E-prescribing

The increased use of e-prescribing has facilitated some changes in the profession of pharmacy and there are more to come. There have been new types of medication errors introduced by e-prescribing and pharmacists need to be aware of these new types of errors so they can adequately minimize or prevent these errors from reaching the patient. It is imperative that pharmacists work together and with other health care providers to reduce medication errors due to e-prescribing.

The IOM report, "To Err Is Human," listed four approaches to improve safety and reduce medical errors (Table 1).[1] Although this report is over 10 years old, the goals outlined by the IOM are still relevant to the present situation regarding e-prescribing. For example, having a reporting system in place for pharmacists to report medication errors due to e-prescribing could be beneficial by allowing the collection of more data regarding the rate of errors in e-prescribing. Furthermore, raising "performance standards and expectations for improvements in safety" for both prescribers and pharmacists regarding e-prescribing could lead to a reduction in errors that reach the patient.[1]

Part of the appeal of e-prescribing is that these systems are supposed to reduce medication errors, however, in a survey done by the Michigan Pharmacists Association, it was found that 40.3 percent of pharmacists responding indicated that e-prescribing had created more errors versus 10.4 percent of pharmacists reporting that e-prescribing had created fewer errors.[16] E-prescribing has the potential to reduce medication errors with improvements from both prescribers and pharmacists and there are actions that pharmacists can take to improve e-prescribing.

According to a statement from the National Community Pharmacists Association (NCPA) regarding e-prescribing, the presence of a learning curve exists for prescribers as they adjust from hand-written prescriptions to electronic prescriptions.[17] This presents an opportunity for pharmacists to improve the use of e-prescribing by providing education to various prescribers and their staff. Pharmacists have the chance to inform prescribers of the new classes of medication errors associated with e-prescribing and show them how reducing these types of medication errors during e-prescribing can benefit the prescriber and their staff. For example, if the prescriber reduces the transmission of incorrect electronic prescriptions then pharmacists will be calling the office less to clarify and correct the errors, which will result in fewer interruptions for the prescriber and staff and more productivity on their end. The pharmacist can even suggest methods to reduce errors if he or she has a good relationship with the prescriber and feels comfortable doing so. Some suggestions include, but are not limited to, having the prescriber visually verify the electronic prescription (especially if generated by an agent of the prescriber) before it is sent and instituting a double-check of information entered into the electronic prescription with information in the

Table 1. The Four-Tiered Approach to Improving Patient Safety[1]

1. Establishing a national focus to create leadership, research, tools and protocols to enhance the knowledge base about safety.
2. Identifying and learning from errors by developing a nationwide public mandatory reporting system and by encouraging health care organizations and practitioners to develop and participate in voluntary reporting systems.
3. Raising performance standards and expectations for improvements in safety through the actions of oversight organizations, professional groups and group purchasers of health care.
4. Implementing safety systems in health care organizations to ensure safe practices at the delivery level.

patient's medical chart before the electronic prescription is sent.

Another way that pharmacists can help to minimize or prevent medication errors associated with e-prescribing is to simply be aware of these new types of errors and their prevalence to improve their diligence. A survey done by the Michigan Pharmacists Association shows medication errors that are seen "sometimes" and "frequently" on electronic prescriptions, rather than "rarely" or "never" (Table 2).[16] Some of these types of medication errors sent by e-prescribing will be apparent and easily recognizable, while others may be harder for the pharmacist to catch. Hence, increased diligence from the pharmacist regarding electronic prescriptions and extra review by the pharmacist of all the electronic prescriptions received is needed. For example, a prescriber sends over an electronic prescription for a patient and has selected the extended-release version of a drug, while the patient was previously on the immediate-release version of that same drug. The prescriber has written for an acceptable dose of the extended release version and there is no other information on the prescription to indicate that an error has been made. However, the prescriber never intended to switch the patient to the extended-release drug, but the wrong drug was chosen during the e-prescribing process. So how can the pharmacist prevent this error from reaching the patient? If the pharmacist is more aware that these types of errors can occur with e-prescribing and is diligent while verifying prescriptions, the pharmacist will realize there is the possibility of an error with this electronic prescription and can take appropriate action. Pharmacists can take actions to minimize medication errors similar to this scenario, along with the other new types of errors related to e-prescribing and therefore improve patient safety. For instance, the pharmacist can ask patients who have had medication or dose changes sent over electronically if they were expecting such a change or if the prescriber mentioned anything to them about a change. Pharmacists also have the option of calling the prescriber to verify that he or she did mean to select that drug or that dose of medication.

Conclusion

Overall, pharmacists play a key role in reducing medication errors associated with e-prescribing. Pharmacists, by working together and with other health care providers, can help improve e-prescribing and enhance patient safety. E-prescribing has the opportunity to decrease medication errors and streamline the prescribing and dispensing process if pharmacists and other health care providers can work together to minimize the new types of medication errors that electronic prescribing has created.

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Table 2. Survey by the Michigan Pharmacists Association Regarding e-Prescribing[16]

Question 18: *"What is/are the biggest challenge(s) regarding e-prescribing for your pharmacy today (if applicable, select more than one)."*

The option "Prescribing errors" was chosen by 81.6% of respondents.

Question 19: *"Clinically, has e-prescribing led to any types of errors?"*

76.9% of respondents answered "yes".

Question 21: A follow-up question. *"Please specify if you have seen these types of errors on e- prescriptions (please elaborate)."*

The percentage of respondents that responded "sometimes" or "frequently" (as opposed to "never" or "rarely") was as follows:

Wrong patient	19%
Wrong medication	62%
Wrong dose	69%
Wrong route	42%

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