DRUG FORMULARY REVIEW™
Utilization, Criteria and Outcomes

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IN THIS ISSUE

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International societies release historic guidelines for treating sepsis

Goal is to reduce mortality rate by 25% in five years

An international group of critical care professionals has developed the first evidence-based recommendations ever to address the treatment of patients with sepsis.

"There is now a gold standard of care for the management of sepsis," says **Mitchell M. Levy**, MD, FCCP, FCCM, associate professor of medicine at Brown University School of Medicine in Providence, RI, and medical director of the Medical Intensive Care Unit at Rhode Island Hospital. Levy is one of the guidelines' authors.

The guidelines are the result of a collaboration that began in 2002, when the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the International Sepsis Forum came together to form the "Surviving Sepsis Campaign." Data in the literature, both specific for sepsis and for general disease management in the intensive care unit, suggested that the societies could improve survival in sepsis by creating guidelines and an international standard of care, Levy says. The campaign has been endorsed by 11 of the world's leading critical care and infectious disease societies. Eli Lilly & Co., Baxter International, and Edwards Lifesciences Corp. added support with unrestricted educational grants.

The guidelines are remarkable for several reasons, Levy reports. First, there has never been a comprehensive set of guidelines for the overall treatment of sepsis. Second, and probably even more important, is the number of international infectious disease and critical care societies that have endorsed it, he adds. "It is historic that we have such a broad consensus of disciplines internationally signing on to a single set of guidelines."

The campaign has a threefold goal, Levy explains. The societies first wanted to increase public and clinician awareness of sepsis. Next, they wanted to create the set of consensus guidelines for sepsis management.

To accomplish this, the group held a consensus conference of about 45 opinion leaders in critical care and infectious diseases. The leaders came to the conference prepared, Levy says. "They did a thorough evidence-based review of the literature for each of their topics." The group

went from the meeting to publication of their recommendations in a few short months. "We were determined not to sit on this because we think it is highly important."

The guidelines are detailed and comprehensive. Some of the recommendations include:

- More aggressive recognition and diagnosis of sepsis in all hospital departments.
- Monitoring of central venous oxygen saturation levels.
- Empiric, timely antibiotic therapy to fight the underlying infection.
- Maintenance of adequate blood pressure through intravenous fluids and/or medications.
- When localizable, removal or reduction of the source of the infection (for instance, removal of a potentially infected catheter or drainage of an abscess).

One of the highest impact points in the guidelines for pharmacists is the early institution of antibiotics, Levy says. "We have always said that. Now we are saying that within the first hour or two, the right antibiotics — or at least antibiotics — should be given to patients who are septic." Guidelines also exist for the number of blood cultures and for the use of steroids. "It is important for pharmacists to know which drugs are being recommended in the guidelines and [when to give them]."

The guidelines were initially presented at the 33rd Annual Critical Care Congress of the Society for Critical Care Medicine (SCCM) in Orlando, FL. They were next published in the March issues of both *Critical Care Medicine* and *Intensive Care Medicine*. The guidelines also will be posted online, free of charge, at the SCCM site and the sites of participating organizations.

Reaction among critical care professionals has been more positive than expected, Levy says. "We thought we would get a lot of 'I don't know if I agree with this and that.' Instead, we have run into a very high level of acceptance."

The third facet of the goal, and next step, is to put these guidelines into practice and change clinician behavior. The campaign hopes to reduce the sepsis mortality rate by at least 25% over the next five years, Levy reports. Sepsis now kills about 1,400 Americans daily.

"Phase III is moving into a collaborative of different hospitals where we are going to take the guidelines, turn them into what are called 'change bundles,' and find a way to bring them to the bedside of critically ill patients," he says. Chart review will identify and track change in practice and clinical outcomes.

These guidelines are subject to change, the authors say. "New interventions will be proven and established interventions, as stated in the current recommendations, may need modification." The authors expect to formally update the guidelines yearly. ■

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Systematic approach taken in evaluating sepsis drug

Focus on disease state, not drug management

After the results of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial were published in 2001, many institutions established criteria for use of drotrecogin alfa (activated) that were similar to

Table: An evidence-based approach to evaluating the safe, rational, cost-effective use of drotrecogin alfa (activated) in clinical practice

Safety:		
	Outcome of value: *Incidence of bleeding*	
	Outcome influencers:	**Definition of bleed**
		Relationship to procedure
		International normalized ratio (INR)
		Hepatic dysfunction
		Prothrombin time (PT)
Rationale:		
	Outcome of value: *Mortality*	
	Outcome influencers:	**Number of organ dysfunctions**
		Time to treat
Duration of therapy:		
		APACHE II score
		Number of comorbidities
Cost-effective:		
	Outcome of value: *Cost per life saved*	
	Outcome influencers:	**Intensive care unit length of stay**
		Hospital length of stay
		Ventilator days
		Vasopressor days

the inclusion criteria used in the trial. Institutions, however, then had to decide how to evaluate the criteria and the outcomes of patients with sepsis. At one institution, a broad, systematic approach to that evaluation was taken.

Hospitals especially want to make sure that they are using drotrecogin alfa on the patients who will benefit most from it, says **Shane Winstead**, PharmD, intensive care unit (ICU) clinical pharmacy specialist in the Department of Pharmacy Services, and assistant professor at the College of Pharmacy, University of Kentucky Chandler Medical Center in Lexington. First, the medical center set up the criteria used in PROWESS for drotrecogin alfa (activated). One change was made, however, based on the approval of the expensive drug from the U.S. Food and Drug Administration (FDA).

"PROWESS included all patients who presented with specific criteria for severe sepsis with at least one organ failure," she says. "But when the FDA looked at the product, they only approved it for patients with high-risk of mortality." Therefore, Winstead and her colleagues decided to use the drug on the sicker patients, such as those with more organ dysfunction.

When criteria like these are set up, it is key to follow up later to see if they are being followed, Winstead says. "It's for the cost and the safety of the drug — to make sure that we are selecting patients who aren't high risk for bleeding and that we are minimizing our adverse events."

Winstead collaborated with Craig Martin, PharmD, antimicrobial management team pharmacist at the University of Kentucky and Jeff Durthaler, MS, RPh, outcomes liaison for Eli Lilly & Co. in Indianapolis. Their systematic approach began by looking at "safe, rational, and cost-effective" in terms of the drug and then defining one outcome of value that would be the best predictor of those three endpoints, she explains. "For each outcome, we decided on outcome influencers, those things that influenced whether the outcome would be positive or negative."

They chose bleeding, mortality, and total cost per life saved as the outcome of value for the safe, rational, and cost-effective endpoints. Mortality was important because many institutions are finding their rates to be higher than what was reported in PROWESS, Winstead says. "We were trying to look at 'Is that OK?' Our target may not be the PROWESS outcome, but how close do we accept it around that outcome?"

Their evaluation found overall positive results but also specific areas that needed improvement. In terms of safety, they were happy with the outcomes and the patients' adverse events, she notes. "We haven't had any severe bleeding in any of our patients." A chart review, however, found more cases of moderate bleeding than they had expected.

"It is really not that clinically significant. The patients have some oozing around catheter sites or bruising; they don't require transfusions," she says. A closer look found that staff weren't following the package insert 100% of the time for those kinds of procedures. "We saw areas of improvement for our institution. Others may find that they are treating patients at a higher risk of bleeding such as coagulopathies."

Winstead and her colleagues did find their mortality rate was still within what they determined to be an acceptable range for the type of patients that they had. "When we broke that

down to the influencers of mortality, we were looking at organ dysfunction, time to treat, APACHE II scores, and patients who have comorbidities. We were happy to see that we were treating patients early after onset of initial organ dysfunction, within 16 hours."

Institutions need to pay attention to the time to treat, she adds. "Are they waiting too long to start the drug? Or are they catching patients further along in their illness to where the institutions may have had better outcomes if they had been more aggressive early on?" Winstead says.

Winstead and her colleagues found that their higher mortality rate compared to PROWESS may be a reflection of treating a larger number of patients with comorbidities. "It's a difficult call from patient to patient about how aggressive you are going to be. We did identify a few patients who were probably far enough along in chronic illnesses that treating the acute illness really didn't change that outcome."

In the cost-effective area, they looked at factors such as length of stay in the ICU and in the hospital. Winstead says they are trying to make improvements by implementing a more standardized approach to management in these patients, supportively and outside the use of the drug. "The big way to bring the cost down in these patients is to try to shorten the patients' ICU and hospital stay."

Overall, Winstead believes that the drug is giving them some advantage, and she is satisfied with the approach they took to evaluating its use. "I liked how we determined the one outcome that we thought was most indicative of how we wanted to look at the drug and how we identified some influencers for each outcome." The approach is systematic in that they could take their results, find out what drove those results, and then use that information to target areas for improvement **(see Table, p. 27)**.

"We didn't just focus on the drug itself," she says. "We tried to pull back and look at the disease state and how we managed that as a whole and how that impacted outcomes in our patients." ■

FDA to require bar codes on many drugs and biologics

Rule may spur centers to add bedside scanning

Pharmacists now can expect thousands of drugs and biological products to have bar codes on their labels by 2006.

The U.S. Food and Drug Administration (FDA) issued the final rule in February that requires linear bar codes to be included on most prescription drugs and on certain over-the-counter drugs that are commonly used in hospitals and ordered by physicians. Each bar code for a drug will have to contain, at a minimum, the drug's National Drug Code (NDC) number.

"We think it is a great step forward in ensuring patient safety," says **Mary Beth Navarra**, RN, MBA, director of medication safety for McKesson Corp., a San Francisco, CA-based health care services and information technology company.

"Everyone would liked to have seen lot number and expiration date included, but the reality is that NDC will certainly help prevent medication errors at the bedside by enabling caregivers to scan the bar codes and compare them to the patient profiles."

The rule also requires the use of machine-readable information on container labels of blood and blood components intended for transfusion. These labels contain FDA-approved, machine-readable symbols identifying the collecting facility, the lot number relating to the donor, the product code, and the donor's blood group and type.

The final rule applies to most drug manufacturers, repackers, relabelers, private label distributors, and blood establishments. New medications covered by the rule will have to include bar codes within 60 days of their approval. Most previously approved medicines and all blood and blood products will have to meet the April 26, 2006, compliance date, which is two years from the rule's effective date.

The FDA estimates that when the bar code rule is fully implemented, it will help prevent nearly 500,000 adverse events and transfusion errors over 20 years. The economic benefit during that time of reducing health care costs, patient pain and suffering, and lost work time due to adverse events is estimated to be $93 billion.

Rule gives incentive for bedside scanning

The new rule will encourage health care providers to implement point-of-care systems for bedside scanning, Navarra says. Few facilities do it now. Only 1.5% of the hospitals reported that they scanned bar codes at the bedside, according to the results of the 2002 American Society of Health-System Pharmacists national survey of

pharmacy practice in hospital settings.

"People believe that one of the barriers to implementing systems for bar code scanning is that not all meds have bar codes on them and that there is no standard," she says. "We hope this will help spur the implementation."

Some of the facilities that implement the technology have reported large reductions in medication errors. For instance, the introduction of a point-of-care bar code scanning system at the University of Wisconsin Hospitals and Clinics in Madison resulted in an 87% reduction in medication administration errors. Of the errors observed in the pre-implementation phase of the study, 44% involved medications given at the wrong time, 21% involved the wrong dose of a medication, 15% resulted from omission of a medication, 15% used the wrong dosage form, and 5% involved use of an incorrect drug.

In addition to reducing medication errors, a point-of-care system for bedside scanning creates a mobile medication administration record for the nurses and pharmacists, Navarra adds.

"Nurses will have real-time information at all times — what is ordered for the patients, what has been given. If they walk into a patient's room and the patient asks when he or she last received pain medication, they can answer the question without having to hunt down a paper chart," she points out.

In the process of scanning the bar codes and doing safety checks, the health care providers are creating the electronic documentation of the medications being given, too. "It eliminates the need to paper chart or having to go back and initial medications," she says.

Even with the benefits, health care facilities need to do a thorough evaluation before implementing such a system, Navarra notes. "Hospitals need to take a step back, understand their current process, understand the impact that implementing a system like the point-of-care bedside scanning would have on that process, and begin to redesign and prepare for that kind of implementation."

Remember that the rule will not result in every medication being bar coded, she says. "Although the mandate will increase the number of bar codes, there are still going to be either medications that are patient-specific and prepared in the pharmacy, or other medications that will still have to be labeled.

"There is going to be a lot of interaction between nursing and pharmacy on processes and procedures and how they want to handle things," she continues. "It's a whole new world. You want to automate the process, but you want to take the opportunity to improve it as well." ■

New drug initiatives, task force report announced

The federal government announced several new initiatives recently regarding prescription drugs, as well as the final report from the Counterfeit Drug Task Force:

• The final report from the U.S. Food and Drug Administration's (FDA's) Counterfeit Drug Task Force:

The task force, created in July 2003, met with and heard from security experts, federal and state law enforcement officials, technology developers, manufacturers, wholesalers, retailers, consumer groups, and the general public. In October 2003, the task force issued an interim report that was followed by a public meeting and technology forum where 72 presentations were made.

The report describes specific steps that can be taken now and in the future to protect consumers from counterfeit drugs and to secure the U.S. drug distribution system. Some of these measures include:

— Implementation of new technologies to better protect legitimate drugs against tampering or replacement with counterfeits.

— Adoption of reliable modern track and trace technology, which the FDA has concluded is feasible by 2007, to accomplish and surpass the goals of the Prescription Drug Marketing Act.

— Adoption and enforcement of stronger anti-counterfeiting measures by the state regulators of drug wholesalers and distributors.

The full FDA Counterfeit Drug Task Force Final Report, including more recommendations, can be found at www.fda.gov/oc/initiatives/counterfeit/.

• The Department of Health and Human Services (HHS) has created a task force to advise and assist HHS in determining how drug importation might be conducted safely and its potential impact, positive and negative, on the health of American patients, medical costs, and the development of new medicines.

The task force intends to convene five meetings, one each with representatives from the following groups: consumer groups; professional health care groups; health care purchasers, including

representatives of cities and states; industry associations; and international stakeholders. There also will be a meeting for the general public to provide comments.

The task force will also open a public docket to accept comments. To begin public discussion, the task force will post a set of preliminary questions about the safety and impact of drug importation. The task force will publish proceedings from the stakeholder meetings.

• **The FDA has launched a new web site to help consumers and health professionals find information about FDA-approved drug products.** The new interface, Drugs @ FDA, is a searchable database that includes information on approved prescription drugs, some over-the-counter drugs, and discontinued drugs. Located on the web page of the FDA's Center for Drug Evaluation and Research (CDER), it is the first web resource to offer a comprehensive overview of a drug product's approval history.

The database incorporates information from all parts of CDER's web site, including Consumer Information Sheets, Medication Guides, labeling, and other information for patients. Eventually, information on recalls, warnings, and drug shortages will also be included.

Users can search by drug name or active ingredient to retrieve a complete approval history and accompanying documents for a particular drug product. Users also can find out if therapeutic equivalents exist, including generics for brand name drugs. ■

Pregnant women concerned about taking asthma medications

A national survey shows that 39% of asthmatic women who have been pregnant discontinued using their asthma medication, reduced their dosage, or did both when expecting. However, the survey found that nearly half (46%) of those using an inhaled corticosteroid (ICS) to manage their asthma would plan to continue their ICS during pregnancy if it had a U.S. Food and Drug Administration (FDA) Category B pregnancy rating.

The survey, conducted by the Case Management Society of America (CMSA) in Little Rock, AR, explored attitudes and experiences regarding asthma medication in 501 women of childbearing age (18-44) with asthma. Questions focused in part on women's perceived benefits and risks of using ICSs and other asthma medication prior to and during pregnancy, and their knowledge of the FDA's pregnancy category rating system for medications. The survey was conducted in 2003 by Harris Interactive and sponsored by AstraZeneca.

Among the survey's key findings were:

• **Most women (82%) who use ICSs to manage asthma are concerned about birth defects if they become pregnant.** More than one in three (36%) currently taking an ICS say their concern is strong enough to discontinue use of the drug during pregnancy, an action that is contrary to the National Heart, Lung, and Blood Institute (NHLBI) recommendation for effective control of persistent asthma.

• **More than half (59%) of respondents are not aware of the FDA's pregnancy category rating.** ▼

Many Americans cut dosages to lessen drug costs, AP poll finds

Almost a third of Americans say paying for prescription drugs is a problem in their families, and many are cutting dosages to deal with the crunch, according to a poll by the Associated Press (AP). Nearly two-thirds of those surveyed said the government should make it easier to buy cheaper drugs from Canada or other countries.

The poll conducted for the AP by Ipsos-Public Affairs found that most Americans either take prescription drugs or someone in their family does. Of those, 33% said their families have trouble paying at times. For people having trouble paying their medicine bills, three-fourths say the solution often is to cut back on the dosage.

The high cost of prescription drugs will be an important issue in the presidential campaign, said eight in 10 in the poll. Almost half said it would be "very important."

A separate poll by Ipsos-Insights found that 2% of those who bought prescription drugs in the last six months have bought medicines from Canada or Mexico and brought them back to this country.

The AP-Ipsos poll of 1,000 adults was conducted Feb. 16-18, and has a margin of sampling error of plus or minus three percentage points. ▼

Talks with docs can result in less expensive drugs for patients

Patients who discuss the costs of prescription drugs with their doctors often result in getting a less expensive prescription, according to the results of a recent *Wall Street Journal* Online/Harris Interactive Health-Care Poll.

Two in five adults (43%) say they discussed with their doctors the pros and cons of different prescription drugs that they might prescribe for them. More than half of these people (23% of all adults) also say that they discussed the different costs to them of different drugs their doctors might prescribe. One in seven adults (14%) say their doctor prescribed one drug rather than another because it was less expensive for them.

This study was conducted on-line within the United States between Feb. 2 and 4 among a nationwide cross section of 2,238 adults, ages 18 years and older. Figures for age, sex, race, education, region, and income were weighted where necessary to bring them into line with their actual proportions in the population. Propensity score weighting also was used to adjust for respondents' propensity to be on-line. ▼

Elderly continue to be prescribed inappropriate medication

A recent study shows that elderly people continue to be prescribed potentially inappropriate medications at ambulatory care visits.

The study, published in the Feb. 9 issue of *Archives of Internal Medicine*, compared 1995 and 2000 data from office-based physicians in the National Ambulatory Medical Care Survey and from hospital outpatient departments in the National Hospital Ambulatory Medical Care Survey.

In 1995 and 2000, at least one drug considered inappropriate by the expert panel was prescribed at about 7.8% of ambulatory care visits by elderly patients. At least one drug classified as never or rarely appropriate by the expert panel was prescribed at 3.7% and 3.8% of these visits in 1995 and 2000, respectively. Much of the problem centered on pain relievers and central nervous system drugs. The odds of potentially inappropriate prescribing were higher for visits with multiple drugs and double for female visits. Females, for example, were prescribed more potentially inappropriate pain relievers and central nervous system drugs.

Potentially inappropriate prescribing at ambulatory care visits by elderly patients, particularly women, remains a substantial problem, the researchers conclude. "Interventions could target more appropriate drug selection by physicians when prescribing pain relievers, anti-anxiety agents, sedatives, and antidepressants to elderly patients. Such behavior could eliminate a large portion of inappropriate prescribing for elderly patients and reduce its higher risk for women." ■

New FDA Approvals

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

• *Bevacizumab (Avastin) by Genentech.* The FDA has approved bevacizumab (Avastin) as a first-line treatment for patients with **metastatic colorectal cancer.**

Bevacizumab, a monoclonal antibody, is the first angiogenesis inhibitor to be approved. Bevacizumab was shown to extend patients' lives by about five months when given intravenously as a combination treatment along with standard chemotherapy drugs for colon cancer (the "Saltz regimen," also known as IFL). IFL treatment includes ironotecan, 5-fluorouracil, and leucovorin.

Serious, but uncommon, side effects of bevacizumab include formation of holes in the colon generally requiring surgery and sometimes leading to intra-abdominal infections, impaired wound healing, and bleeding from the lungs or internally. Other, more common side effects are high blood pressure, fatigue, blood clots, diarrhea, decreased

COMING IN FUTURE MONTHS

- Alpha1-blocker formulary review
- A competency assessment tool for drug use policy and drug information
- Multitasking success in pharmacy practice
- The 'unit-specific pharmacist' approach
- Rosevastatin (Crestor) drug evaluation

white blood cells (lowering immunity to diseases) headache, appetite loss, and mouth sores.

• *Pemetrexed disodium (Alimta) by Eli Lilly & Co.* The FDA has approved pemetrexed disodium (Alimta) for use in combination with cisplatin for the treatment of patients with **malignant pleural mesothelioma.** Pemetrexed disodium received a priority review and is designated as an orphan drug. It is the first drug approved for this condition.

The effectiveness of pemetrexed disodium was established in one randomized clinical trial comparing the effects of treatment with pemetrexed disodium given with cisplatin to treatment with cisplatin alone. Patients receiving pemetrexed disodium and cisplatin lived three months longer after randomization than patients given cisplatin alone (12 months vs. nine months). Pemetrexed disodium must be administered with vitamin B_{12} and folic acid supplementation to decrease the incidence and severity of adverse effects.

The most common adverse reactions observed with use of pemetrexed disodium are low white blood count, nausea, vomiting, fatigue, rash, and diarrhea. Patients and caregivers should be encouraged to report the onset of fever, chills, diarrhea, and mouth ulcers immediately, since these symptoms could be a sign of infection, resulting from bone marrow suppression by the drug.

• *Cetuximab (Erbitux), manufactured by ImClone Systems and distributed by Bristol-Myers Squibb Co.* The FDA has approved cetuximab (Erbitux) to treat patients with **advanced colorectal cancer** that has spread to other parts of the body. Cetuximab is the first monoclonal antibody approved to treat this type of cancer and is indicated as a combination treatment to be given intravenously with irinotecan, another drug approved to fight colorectal cancer, or alone if patients cannot tolerate irinotecan.

Cetuximab was approved under the FDA's accelerated approval program. Although treatment with cetuximab has not been shown to extend patients' lives, it was shown to shrink tumors in some patients and delay tumor growth, especially when used as a combination treatment.

Cetuximab can cause serious side effects, usually during the administration of the first treatment, which may include difficulty breathing and low blood pressure. Infrequent interstitial lung disease (ILD) has been reported; however, it is difficult to determine if cetuximab caused ILD. Other more common side effects of cetuximab treatment include acne-like rash, dry skin, tiredness or weakness, fever, constipation, and abdominal pain.

The FDA also approved a test kit, manufactured by DakoCytomation California that is used by doctors to analyze a colon tissue sample. The kit detects a protein in the body (HER-1) that stimulates cancerous tissue cell growth. Presence of this protein indicates that a patient is eligible for colon cancer treatment with cetuximab. ■

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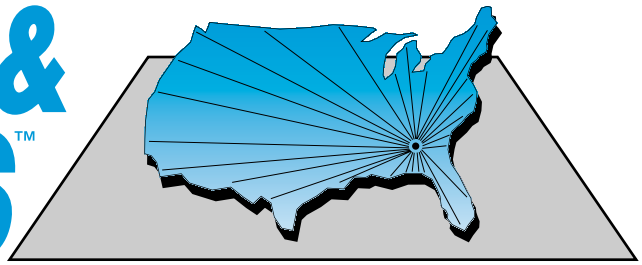

Palonosetron (Aloxi) Formulary Evaluation

Part 2: Clinical Trial Data, Adverse Effects, and Cost Analysis

By **Brian Watkins**, PharmD Candidate
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(Editor's note: This second part of the palonosetron formulary evaluation addresses the available clinical trial, adverse effects, and cost analysis data. For information on mechanism of action, pharmacokinetics, indications, dosage, and administration of palonosetron, please consult the March issue of Drug Formulary Review's Drug Criteria & Outcomes.)

Moderately emetogenic chemotherapy

Trial 1: Palonosetron improves prevention of chemotherapy-induced nausea and vomiting (CINV) following moderately emetogenic chemotherapy: Results of a double-blind randomized Phase III trial comparing single doses of palonosetron with ondansetron.

***Objective*:** To compare the efficacy and tolerability of single, fixed intravenous doses of palonosetron with a single intravenous dose of ondansetron in the prevention of acute and delayed CINV following administration of moderately emetogenic therapy.

***Study Design*:** Multicenter, randomized, controlled, double-blind, double-dummy, stratified, Phase III study, noninferiority study.

***Methods*:**

• 563 patients randomized; palonosetron 0.25 mg (n = 189), palonosetron 0.75 mg (n = 189), ondansetron 32 mg (n = 185).

• Patients had to be 18 years of age or older with histologically or cytologically confirmed malignant disease. The study included patients who were chemotherapy-naïve as well as those who had been treated previously with chemotherapy; all were scheduled to receive moderately emetogenic chemotherapy (any dose of carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, or mitoxantrone; methotrexate > 250 mg/m^2; cyclophosphamide < 1500 mg/m^2; doxorubicin > 25 mg/m^2; or cisplatin < 50 mg/m^2).

• Patients were excluded if they were unable to understand or cooperate with study procedures, used any drug with antiemetic activity within 24 hours prior to treatment and until day five, had evidence of a seizure disorder requiring anticonvulsants, experienced anticipatory nausea and vomiting, or were scheduled for radiation of the upper abdomen or cranium on days 2-6.

• Patients were randomized to receive a single, fixed intravenous dose of either palonosetron 0.25 mg, palonosetron 0.75 mg, or ondansetron 32 mg.

Results

• No patient received pretreatment with corticosteroids. Metoclopramide was the most

Table 5: Trial 1 results: Acute, delayed, and overall complete response

Time Period (hours)	Palonosetron 0.25 mg (n = 189)			Palonosetron 0.75 mg (n = 189)			Ondansetron 32 mg (n = 185)
	%	Palo-Ond (CI = 97.5%)	P	%	Palo-Ond (CI = 97.5%)	P	%
Acute, 0-24	81	1.8-22.8%	0.0085	73.5	-6.1-15.9%	0.3067	68.6
Delayed, 24-120	74	7.5-30.3%	0.001	64.6	-2.4-21.3%	0.0730	55.1
Overall, 0-120	69	7.4-30.7%	0.001	58.7	-3.6-20.5%	0.1192	50.3

commonly administered rescue medication.

• The primary efficacy endpoint was the proportion of patients achieving a complete response (CR; defined as no emetic episode and no use of rescue medication) during the first 24 hours following chemotherapy administration **(see Table 5)**.

• Secondary endpoints examined were the proportion of patients with a CR during the delayed 24-120 hour time period, the cumulative overall 0-120 hour period, and CR rates during successive 24 hour time periods. The proportion of patients achieving complete control (CC; defined as no emetic episode, no need for rescue medication, and no more than mild nausea) for the 0-24 hour, 24-120 hour, and 0-120 hour intervals **(see Table 6)**. Time to first emetic episode, severity of nausea measured daily, time to treatment failure, time to administration and need for rescue medication, patient's global satisfaction with antiemetic therapy, as well as quality of life also were secondary endpoints.

• To demonstrate the noninferiority of at least one dose of palonosetron to ondansetron, the lower boundary of the two-sided 97.5% confidence interval for the difference (palonosetron–ondansetron) between the proportion of patients achieving a CR during the first 24 hours after chemotherapy had to be greater than the preset threshold of -15% difference.

• Palonosetron 0.25 mg was consistently superior to ondansetron ($P \leq 0.05$) in the number of emetic episodes (during the acute, delayed, and overall intervals as well as on study days 2 and 3), proportion of patients with no emetic episodes (during delayed and overall intervals as well as on study days 1-3), and the proportion of nausea-free patients (on study days 3-5).

• Palonosetron 0.75 mg was superior to ondansetron in the proportion of patients with no emetic episodes (during delayed and overall intervals as well as on study day 3) and the proportion of patients with no nausea (on study days 4 and 5).

Trial strengths

— Large multicenter, randomized, double-blind trial.

— Study population included chemotherapy-naïve patients and those who previously had received chemotherapy.

— Study reproduced CR rates for ondansetron similar to those found in other studies.

Trial weaknesses

— Lack of consistency in presentation of the results.

— Results section does not mirror efficacy/outcome measures section.

Authors' conclusions:

• Palonosetron 0.25 and 0.75 mg are similar in overall efficacy.

• A single intravenous dose of palonosetron results in prolonged protection against nausea and emesis following moderately emetogenic chemotherapy.

• Palonosetron proved superior to ondansetron in preventing both acute and delayed CINV following moderately emetogenic chemotherapy. Thus, palonosetron is a significant and important addition to antiemetic therapy.

Trial 2: Palonosetron is active in preventing acute and delayed emesis following moderately emetogenic chemotherapy: Results of a Phase III trial.

***Objective*:** To assess the safety and efficacy of single intravenous doses of palonosetron vs. dolasetron for the prevention of moderately emetogenic CINV.

***Study design*:** Multicenter, randomized, double-blind, parallel, stratified, noninferiority trial.

Methods:

• 569 patients randomized; palonosetron 0.25 mg (n = 189), palonosetron 0.75 mg (n = 189), and dolasetron 100 mg (n = 191).

Table 6: Trial 1 results: Complete control

Time Period (hours)	Palonosetron 0.25 mg (n = 189)	P	Palonosetron 0.75 mg (n = 189)	P	Ondansetron 32 mg (n = 185)
Acute, 0-24		NR		NR	NR
Delayed, 24-120	66.7	0.001		NR	50.3
Overall, 0-120	63.0	0.001	53.4	NR	44.9
Time to treatment failure	46.5 h	< 0.001		NR	19.5 h
Delayed, rescue medication	15.9%	NS	22.8%	NS	24.3%
Overall, rescue medication	18.5%	NS	23.8%	NS	27.0%

NR = not reported; NS = not significant.

Table 7: Trial 2 results: Complete response

Time Period (hours)	Palonosetron 0.25 mg (n = 189)			Palonosetron 0.75 mg (n = 189)			Dolasetron 100 mg (n = 185)
	%	Palo-Dola (CI = 97.5%)	P	%	Palo-Dola (CI = 97.5%)	P	%
Acute, 0-24	63	-1.7-21.9%	0.047	57.1	-7.7-16.2%	0.404	52.9
Delayed, 24-120	54	3.4-27.1%	< 0.003	56.6	-6.0-29.7%	< 0.001	38.7

Note: 31 patients (5.4% of treated patients) received steroids; overall, adverse events were mild with headache and constipation being the most common adverse events across all groups.

• Patients were randomized to receive a single, fixed intravenous dose of either palonosetron 0.25 mg, palonosetron 0.75 mg, or dolasetron 100 mg.

• Following an amendment, patients were allowed to receive 20 mg dexamethasone or 125 mg methylprednisolone prior to chemotherapy at investigator discretion.

• The primary endpoint was 24-hour CR **(see Table 7)**.

• Secondary endpoints included daily and cumulative CR rates for the delayed 24- to 120-hour interval.

Authors' conclusions

• Palonosetron has demonstrated significant activity in preventing both acute and delayed emesis with a single intravenous dose in patients receiving moderately emetogenic chemotherapy.

• Palonosetron was safe and well tolerated.

Highly emetogenic chemotherapy

Trial 3: The efficacy and safety profile of palonosetron in a Phase II study involving chemotherapy-naïve patients undergoing highly emetogenic chemotherapy.

Objective: To assess the safety and efficacy of palonosetron administered over a range of single intravenous doses for the prevention of highly emetic CINV.

Study design: Randomized, double-blind, multicenter, dose-ranging Phase II trial.

Methods

• 161 patients randomized to one of five dose groups, which involved six-dose levels of palonosetron (0.3-1, 3, 10, 30, or 90 mcg/kg). Patients received a single intravenous injection of palonosetron 30 minutes prior to receiving highly emetogenic chemotherapy (cisplatin $\geq$ 70 mg/m^2).

• Dexamethasone was not administered to these patients.

• Safety and efficacy evaluations (CR and CC, **see Table 8 for results**) were recorded in a patient diary during the first 24 hours and then daily for the next six days following palonosetron administration.

Adverse events

• Most adverse drug reactions were mild (83.9%) and considered unrelated to palonosetron (86%).

• The most common adverse events related to study medication were headache (19.3%), constipation (8.7%), dizziness (2.5%), and abdominal pain (2.5%).

***Authors' conclusion*:** Palonosetron was safe and effective as a monotherapy in treating chemotherapy-induced emesis and warranted further study as an antiemetic in patients receiving highly emetogenic chemotherapy.

Trial 4: Palonosetron is effective in preventing acute and delayed CINV in patients receiving highly emetogenic chemotherapy.

***Objective*:** To assess the efficacy and safety of single IV doses of palonosetron 0.25 mg or 0.75 mg vs. ondansetron 32 mg administered 30 minutes prior to highly emetogenic chemotherapy.

***Study design*:** Multicenter, randomized, double-blind, stratified Phase III study.

Methods

• Patients were randomized to receive a single, fixed intravenous dose of either palonosetron 0.25 mg, palonosetron 0.75 mg, or ondansetron 32 mg 30 minutes prior to highly emetogenic therapy (cisplatin $\geq$ 60 mg/m^2).

• 67% of patients in each group also received prophylactic corticosteroids.

• The primary endpoint was 24-hour CR **(see Table 9 for results)**.

***Author's conclusion*:** A single dose of palonosetron prior to highly emetogenic chemotherapy is as effective as a single dose of ondansetron 32 mg for prevention of acute CINV and maybe of greater benefit in preventing delayed CINV after highly emetogenic chemotherapy.

Table 8: Trial 3 results

Time period (hours)	Overall trial outcome (all doses)
Acute, 0-24 h	CR = 46-50% and CC = 39-48%
Delayed, 96-120 h (day 5)	CR = 17-33%

Table 9: Trial 4 results

Time period (hours)	Palonosetron 0.25 mg	P	Palonosetron 0.75 mg	Ondansetron 32 mg	P
Acute, 24	59.2%	NR	65.5%	57.0%	NR
CR 24-48	57.0%	NR	57.8%	49.8%	NR
CR 48-72	61.4%	NR	62.3%	53.4%	NR
TTFE*	> 120 h	0.006	> 120 h	42.7 h	0.006

* Time to first emetic episode
Note: Incidence of adverse drug reactions was the same for all groups.

Adverse drug reactions

To date, palonosetron appears to have a side effect profile similar to other currently available setrons; however, post-marketing surveillance should reveal any side effects that recent clinical trials may not have demonstrated. Also, one potential limitation of palonosetron is its ability to prolong QT and QTc intervals, although the drug has been administered safely to 192 patients with pre-existing cardiac impairment.

Cost analysis

Currently, palonosetron is the most expensive setron at Huntsville Hospital when comparing equivalent single doses; the formulary drug granisetron is the least expensive of the four available agents (ondansetron, dolasetron, granisetron, and palonosetron). The price difference per dose between granisetron and the other agents varies from $60 to $100 per dose.

Recommendations

Nausea and vomiting can be a strong predictor of a patient's decision to continue an efficacious chemotherapy regimen. Palonosetron's pharmacodynamics gives way to a binding affinity 100 times greater than that of any other setron. Kinetically, this drug has an elimination half-life of approximately 40 hours. Together, these properties yield efficacy in preventing both acute and delayed CINV. However, drugs in other classes are generally used first for delayed nausea and vomiting.

Palonosetron has not been compared to other regimens used for CINV, including oral and intravenous granisetron (the HH formulary drug). Benefits of palonosetron and other setron drugs include rapid and durable clinical effectiveness, ease of administration, single fixed dosing, and a favorable side effect profile. Additionally, palonosetron has no dosage adjustment in renal or hepatic impairment, and a low potential for drug interactions. Palonosetron is considerably more expensive than granisetron oral or IV in equivalent dosages (see cost summary section). As with other setrons, potential limitations of palonosetron include the ability to prolong the QT and QTc intervals.

Palonosetron should not be added to the formulary at this time. To date, palonosetron appears at least comparable to other setrons in the prevention of CINV, and shows positive results in preventing delayed symptoms.

However, greater experience with this drug through post-marketing surveillance will give a clearer picture with respect to the safety and efficacy of this new therapeutic option. Orders for palonosetron should be converted to granise-tron according to the following dosage equivalents: palonosetron 0.25 mg IV for CINV be interchanged to either granisetron 1 mg IV or 2 mg oral tablet.

Resources

• MGI Pharma. Palonosetron (Aloxi) [formulary information request] Bloomington, MN; 2003.

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• Markman MR, Peterson G, Kulp B, et al. Effectiveness of serotonin-receptor antagonist antiemetic therapy over successive courses of carboplatin-based chemotherapy. *Gynecol Oncol* 2002;85:435-437.

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