Sustol (Granisetron) First Extended-Release 5-HT₃ Receptor Antagonist Approved for the Prevention of Acute and Delayed CINV

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Of the potential side effects of chemotherapy, nausea and vomiting remain among the most fear-inducing events.¹ If appropriate prophylaxis were not provided, more than 70% of patients with cancer who receive chemotherapy would have nausea and/or vomiting.²

Chemotherapy-induced nausea and vomiting (CINV) can have a myriad of clinical consequences for patients, their families, and the healthcare system, including early treatment discontinuation; nonadherence to chemotherapy treatment; problems with appetite and eating, which can lead to nutritional deficits; impaired daily functioning; decline in performance status; impaired health-related quality of life; more frequent physician office visits; emergency department admissions; and higher direct and indirect costs of care.²⁻⁴

The economic costs associated with CINV are significant. A retrospective assessment of more than 19,000 patients with cancer who received highly emetogenic chemotherapy or moderately emetogenic chemotherapy (MEC) with CINV prophylaxis showed that nearly 14% of patients needed CINV-associated care—0.2% for acute-onset CINV, and 13.7% for delayed-onset CINV.⁴ These CINV-associated visits typically required inpatient care (64%) rather than outpatient care (26%) or emergency department care (10%).⁴ The average cost per patient for these CINV-associated visits ranged from $918 to $7448, with the highest per-patient cost for those who required inpatient care.⁴

The incidence and severity of CINV are influenced by the chemotherapy regimen used, including the type of agent, route of administration, and dosage. Patient-related factors can also contribute to CINV, including age, sex, history of CINV, emesis during pregnancy, motion sickness, alcohol use, tumor burden, anxiety, concomitant medication and medical conditions, and inadequate hydration.²⁻⁵

CINV is classified into 3 categories—acute-onset CINV, which occurs within 24 hours of initial administration of chemotherapy; delayed-onset CINV, which occurs 24 hours to several days after initial treatment; and anticipatory CINV, which is triggered by thoughts or anxiety that patients often associate with previous chemotherapy.

The management guidelines for CINV focus on the emetogenic potential of the chemotherapy drug, categorizing drugs and regimens into risk groups. The National Comprehensive Cancer Network (NCCN) guidelines provide examples of agents in each category. Highly emetogenic chemotherapy drugs include cisplatin and dacarbazine, moderately emetogenic agents include doxorubicin and carboplatin, and low-risk to minimally emetogenic agents include docetaxel and fludarabine, respectively.³

Combination antiemetic regimens are the standard of care for controlling CINV.⁶ Examples of antiemetic drugs that are available in the United States are summarized in Table 1.

Table 1    Currently Available Antiemetic Drugs for CINV Prevention

<table>
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<th>Drug type</th>
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| 5-HT₃ receptor antagonists | Dolasetron (Anzemet)  
Granisetron (Kytril [oral, IV], Sancuso patch)  
Ondansetron (Zofran)  
Palonosetron hydrochloride (Aloxi)  
Tropisetron (Navoban) |
| NK₁ receptor antagonists | Aprepitant capsules (Emend)  
Fosaprepitant dimeglumine for injection (Emend)  
Rolapitant (Varubi) |
| Combination agents | Netupitant/palonosetron (Akynezo) |
| Various types | Benzodiazepines  
Butyrophenones  
Cannabinoids (nabilone, dronabinol)  
Dexamethasone  
Metoclopramide  
Olanzapine  
Phenothiazines |

5-HT, indicates 5-hydroxytryptamine; IV, intravenous; NK₁, neuropeptide 1.

lines. These groups broadly agree on the majority of key issues.

For highly emetogenic chemotherapy, including combination therapy with anthracycline and cyclophosphamide, the guidelines recommend triple therapy with a 5-hydroxytryptamine (5-HT3) receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) receptor antagonist.

For MEC regimens, the MASCC/ESMO guidelines recommend double therapy with a 5-HT3 receptor antagonist and dexamethasone. Because dose intensity of chemotherapy regimens is important, particularly in early-stage disease, guideline recommendations for highly emetogenic chemotherapy should be followed when nausea and vomiting are not decreased by recommended therapy for MEC.

For low-risk emetogenic chemotherapy, a 5-HT3 receptor antagonist or dexamethasone monotherapy is adequate. For minimally emetogenic chemotherapy, routine prophylaxis is not recommended.

Although the majority of patients with cancer are protected from CINV with antiemetic drug combinations, some patients still experience nausea and/or vomiting. Improved adherence to antiemetic guidelines, as well as more effective antiemetic drugs, are therefore needed.

**Granisetron Extended-Release Injection Approved for CINV Prevention**

On August 10, 2016, the US Food and Drug Administration (FDA) approved granisetron (Sustol; Heron Therapeutics) extended-release (ER) injection, in combination with other antiemetic drugs, in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of MEC or anthracycline plus cyclophosphamide combination chemotherapy regimens. Granisetron ER injection uses polymer-based drug delivery technology to maintain therapeutic levels of granisetron for ≥5 days.

The clinical development program for granisetron ER included a large, guideline-based clinical trial with more than 700 patients who were undergoing MEC or anthracycline plus cyclophosphamide combination chemotherapy. Granisetron ER was evaluated in the prevention of acute-onset and delayed-onset CINV, demonstrating noninferiority to palonosetron hydrochloride.

“Despite advances in the management of CINV, up to half of patients receiving chemotherapy can still experience CINV, with delayed CINV being particularly challenging to control. In our experience, other 5-HT3 receptor antagonists, including palonosetron, are generally effective for 48 hours or less. Sustol, due to its extended-release profile, represents a novel option that can protect patients from CINV for a full 5 days,” said Ralph V. Boccia, MD, FACP, Medical Director, Center for Cancer and Blood Disorders, Bethesda, MD.

Jeffrey Vacirca, MD, FACP, Chief Executive Officer and Director of Clinical Research, North Shore Hematology Oncology Associates and Vice President, Community Oncology Alliance, East Setauket, NY, commented on the approval, “The Sustol clinical trial populations and results are highly representative of cancer patients in our real-world clinical practice.”

**Mechanism of Action**

Granisetron is a selective 5-HT3 receptor antagonist with minimal affinity for other serotonin receptors, including alpha1-, alpha2-, or beta-adrenoreceptors; dopamine; histamine; benzodiazepine; and opioid receptors.

The 5-HT3-type serotonin receptors are located peripherally on vagal nerve terminals, as well as centrally in the chemoreceptor trigger zone. After receipt of specific chemotherapy drugs, serotonin is released, stimulating 5-HT3 receptors and inducing vomiting.

**Dosing and Administration**

The recommended dose of granisetron ER is 10 mg administered subcutaneously. Granisetron ER injection should be given in combination with dexamethasone ≥30 minutes before starting MEC or anthracycline plus cyclophosphamide combination chemotherapy on the first day of chemotherapy. Because of its ER properties, granisetron ER should not be administered more frequently than once every 7 days.

For patients receiving MEC, the recommended dose of dexamethasone is 8 mg administered intravenously on day 1. For patients receiving anthracycline and cyclophosphamide combination chemotherapy, the recommended dose of dexamethasone is 20 mg given intravenously on day 1, followed by 8 mg orally twice daily on days 2, 3, and 4.

When granisetron is combined with an NK1 receptor antagonist, the recommended dose of dexamethasone should be determined based on the NK1 receptor antagonist’s prescribing information.

Granisetron ER is delivered through a novel technology to maintain therapeutic levels of the drug for ≥5 days.

Granisetron ER should not be administered with successive emetogenic chemotherapy cycles for more than 6 months.

**Granisetron Extended-Release Distribution**

Granisetron ER is distributed through several distribution networks and specialty pharmacies, including ASD Healthcare, Cardinal Health Specialty Pharmaceutical Distribution, McKesson Plasma and Biologics, McKesson Specialty, and Oncology Supply.
A Pivotal Clinical Trial

In a randomized, multicenter, double-blind, parallel-group study, a single dose of granisetron ER injection (10 mg subcutaneously) was compared with a single dose of intravenous (IV) palonosetron hydrochloride (0.25 mg) in patients with cancer who were undergoing MEC or anthracycline plus cyclophosphamide combination chemotherapy. Each agent was administered 30 minutes before chemotherapy on day 1. Patients also received 8 mg or 20 mg of IV dexamethasone on day 1, depending on the chemotherapy regimen. Patients who received 20 mg of IV dexamethasone also received oral dexamethasone 8 mg twice daily on days 2, 3, and 4.11,12

Of the 733 patients included in this study, 371 received granisetron ER and 362 received palonosetron.11 The majority of patients were female (79%) and Caucasian (63%).11 The patients’ mean age was 57 years (range, 22-91 years).11 Their chemotherapy regimens included MEC (55%), most often carboplatin and paclitaxel, or anthracycline plus cyclophosphamide combination therapy (45%).11

The primary end point was the proportion of patients who achieved complete response, defined as no emetic episodes (vomiting or retching) and no use of rescue medication, during the acute phase (0-24 hours) and the delayed phase (>24-120 hours) after chemotherapy in cycle 1.

The noninferiority of granisetron ER injection to palonosetron hydrochloride was demonstrated in the acute and delayed phases of MEC or anthracycline plus cyclophosphamide combination therapy.11 Of the 200 patients who received granisetron ER injection and MEC, 83% achieved complete response during the acute phase, and 69% achieved complete response during the delayed phase. Of the 200 patients who received palonosetron hydrochloride and MEC, 89% achieved complete response during the acute phase, and 70% achieved complete response during the delayed phase (Table 2).

Adverse Events

The safety of a single 10-mg subcutaneous dose of granisetron ER was evaluated in 2 clinical trials involving more than 900 patients with cancer. Dexamethasone was coadministered with granisetron ER in both studies, and an NK1 receptor antagonist was coadministered with granisetron ER in one of the studies.11

Injection-site reactions were the most common group of adverse reactions reported by patients receiving granisetron ER.11 In the first study, 37% of 468 patients who received granisetron ER had injection-site reactions, including bruising or hematoma (22%), erythema (11%), nodule (11%), tenderness (4%), and pain (3%).11

In the second study, patient diaries were used to collect injection-site reaction information daily. Among 456 patients, 62% had injection-site reactions, including bruising or hematoma (45%), tenderness (27%), pain (20%), nodule (18%), erythema (17%), and swelling or induration (10%).11

Patients in both studies may have had ≥1 types of injection-site reactions; 213 of 924 (23%) patients had ≥3 types of injection-site reactions.11

Other adverse reactions observed in ≥3% of patients receiving granisetron ER included constipation, fatigue, headache, diarrhea, abdominal pain, insomnia, dyspepsia, dizziness, ashenia, and gastroesophageal reflux.11

Notable adverse reactions reported in <3% of patients receiving granisetron ER included syncope, elevation of serum transaminase levels, pancreatitis, atrial fibrillation, somnolence, flushing, and hypersensitivity reactions.11

Contraindications

Granisetron ER is contraindicated in patients who have hypersensitivity to granisetron, to any of its components, or to any other 5-HT3 receptor antagonist.11

Warnings and Precautions

Infections at the injection site occurred in 0.4% of patients with cancer in clinical trials of granisetron ER; all patients received antibiotics and had complete resolution.11 Bruising and/or hematomas at the injection site were deemed severe in 3% of patients; patients taking anticoagulant and antiplatelet medications are at an increased risk for severe bruising.11 Bleeding at the injection site occurred in 4% of patients who received granisetron; bleeding for ≥5 days was reported in 1% of patients.11

Pain and/or tenderness severe enough to require pain medication, interfere with activity level, or cause significant discomfort at rest was reported in 2% of patients who received granisetron ER.11 Nodules at the injection site
occurred in 18% of patients who received granisetron ER; 6% of patients had nodules that persisted for >21 days.11 Overall, 20% of patients who received granisetron ER reported constipation compared with 13% to 15% of patients who received a 5-HT3 receptor antagonist in clinical trials.11 Granisetron ER may mask a progressive ileus and/or gastric distention, particularly in patients who recently underwent abdominal surgery.11

Hypersensitivity reactions, including anaphylaxis, have been reported in patients who received granisetron ER and who had a hypersensitivity to other 5-HT3 receptor antagonists. Hypersensitivity reactions may occur ≥7 days after the administration of granisetron ER, and may have an extended course.11 The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists and is associated with the concomitant use of selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and other agents. Patients who receive granisetron ER and other serotoninergic drugs should be monitored for serotonin syndrome.11

Use in Specific Populations
There are no adequate and well-controlled studies of granisetron ER in pregnant women. Whether granisetron ER is present in human breast milk is not known.11 The safety and effectiveness of granisetron ER have not been established in patients aged <18 years.11 The efficacy of granisetron ER, as well as the nature and frequency of adverse events, were similar between elderly patients and younger patients.11 Granisetron ER should not be administered in patients with severe renal impairment. Granisetron ER should not be given more frequently than once every 14 days for patients with moderate renal impairment.11

Conclusion
Granisetron ER injection is the first 5-HT3 receptor agonist to receive FDA approval for the prevention of CINV. When used in combination with other antiemetic drugs, granisetron ER offers an effective and safe alternative for patients undergoing initial and repeated courses of MEC or anthracycline plus cyclophosphamide combination chemotherapy. Using a novel drug delivery technology to maintain therapeutic levels of granisetron for ≥5 days, this long-acting agent is an important new treatment option for patients with cancer, in part because adherence to consensus antiemetic guidelines remains low. As a single injection, the use of granisetron ER may prevent acute and delayed CINV associated with MEC or with anthracycline plus cyclophosphamide combination chemotherapy.

References