

Specialty Pharma Opportunities in Cancer Supportive Care: A Look at Anti-Emetic Therapy

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) remains one of the most common and distressing side effects of cancer treatment. The current market size of CINV therapeutics is more than \$1.5 billion in the US alone.¹ An estimated 70% to 80% of patients receiving chemotherapy experience some level of nausea and vomiting.² Acute CINV significantly reduces quality of life during treatment, and delayed CINV continues to be an issue after patients return home following their treatment, affecting their ability to perform daily activities. Furthermore, metabolic disturbances, such as electrolyte imbalances and/or dehydration may occur due to CINV, as well as tearing of the esophageal mucosa, rehospitalization, increased medical costs, and increased time commitments by healthcare providers for the management of events caused by CINV. However, one of the most disconcerting consequences of CINV is the tendency of up to 50% of the patients to refuse subsequent

treatment for their disease because of the distress and/or significant reduction in quality of life caused by CINV, ultimately resulting in suboptimal delivery of

treatment for their cancer.³

Although clinical practice guidelines for the prevention and treatment of CINV have improved over time, actual adherence in this regard lags behind (Figure 1). Improvement in risk assessment and stricter adherence to guidelines for the prevention and management of both acute and delayed CINV, particularly for initial courses of treatment, may ultimately lead patients to an improved quality of life during therapy, a reduction in time spent by healthcare providers addressing CINV, and ultimately, a higher compliance rate by patients to optimal therapeutic doses for the management of their disease.⁴

Emesis Classification & Physiology

CINV is classified into three separate phases: acute, delayed, and anticipatory.⁵

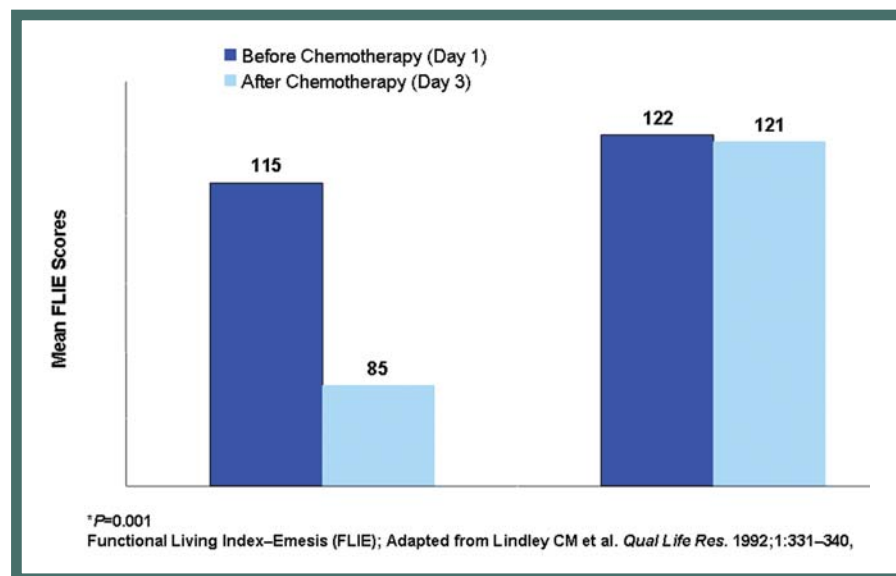


Figure 1. Chemotherapy-Induced Emesis Nausea & Vomiting (CINV) – Impact on Health-Related Quality of Life.

Acute CINV is defined as nausea and/or vomiting that occurs within 24 hours of treatment; delayed CINV is defined as nausea and/or vomiting that occurs after the first 24 hours of treatment and up to 120 hours following treatment; and anticipatory CINV is defined as nausea and/or vomiting that occurs prior to the delivery of subsequent courses of therapy. Breakthrough emesis refers to vomiting that occurs despite optimal prophylactic anti-emetic therapy; however, breakthrough emesis is difficult to assess, as no substantial studies have gathered information to differentiate between true breakthrough emesis and inadequate prophylactic anti-emetic therapy.

The physiology behind CINV remains complex, with many biological pathways contributing to its development, several of which are currently under investigation. It is important to recognize that nausea and vomiting are two distinct entities. Nausea is a feeling characterized by the urge to vomit. It is characteristically reported as an extremely unpleasant and uncomfortable sensation, often accompanied by tachycardia, sweating, flushing, and/or restlessness. Vomiting is the actual propulsion of stomach contents through the esophagus and out of the mouth.

CINV is triggered through complex interactions between neurotransmitters and receptors located in both the peripheral and central nervous systems. Several different neurotransmitters are involved in CINV, including serotonin, dopamine, acetylcholine, histamine, and substance P to name a few. Acute emesis is hypothesized to originate during the release of serotonin into the gastrointestinal (GI) tract post-chemotherapy, leading to stimulation of the 5-HT3 receptor in the central nervous system, which triggers a nauseous reflex – hence, the usefulness/

efficacy of the 5-HT3s in acute emesis. Delayed emesis on the other hand, seems to be mediated by the activation of the substance P/neurokinin(NK)1 receptors – hence, the efficacy of a substance P/NK1 receptor antagonist (aprepitant – Emend®) in delayed emesis.⁶

Incidence of CINV & Current Treatments

Several studies have indicated that physicians and nurses routinely underestimate the incidence of delayed nausea and vomiting (Figure 2). The significant discrepancy between the perceived incidence versus the actual incidence of delayed CINV may be partly due to the fact that patients experience delayed CINV while at home and may not be reporting the side effect to the healthcare providers.⁷

Several different types of anti-emetics are available today, including 5-HT3 receptor antagonists, corticosteroids, D2 receptor antagonists, and NK-1 receptor antagonists, with newer and more effective agents continuing to emerge.⁸ The biggest breakthrough in anti-emesis was the development in the 1990s of 5-HT3 inhibitors, which block the 5-HT3 receptors at both peripheral and central sites from binding of neurotransmitters. 5-HT3 inhibitors are among the most widely used and effective anti-emetic agents for CINV. 5-HT3 inhibitors are highly effective in prevention or management of acute CINV, particularly in highly or moderately emetogenic chemotherapy agents. A comparative summary of the 5-HT3 inhibitors is provided in Table 1.

The use of corticosteroids, along with a 5-HT3 receptor antagonist, is generally recommended for controlling acute emesis

induced by a highly emetogenic drug, while a combination of corticosteroids with metoclopramide or a 5-HT3 receptor antagonist is recommended for delayed emesis. Although it was previously thought that 5-HT3 inhibitors were only useful in the management of acute CINV, the 5-HT3 inhibitor Aloxi® is the first approved drug in its class for the prevention of delayed CINV. This benefit is likely due to palonosetron's longer half-life and high receptor binding for the 5-HT3 receptor (Table 1). Some researchers have questioned whether Aloxi's prevention of delayed CINV is truly pharmacologic or simply a carryover effect. A carryover effect is the most plausible scientific explanation because there is no body of evidence to show that palonosetron has a different mechanism of action than the other 5-HT3 inhibitors. Hence, a drug delivery system capable of maintaining sustained levels up to 5 days for any of the 5-HT3 inhibitors can overcome the shortcomings of a short half-life, while keeping the 5-HT3 receptors saturated, and should show benefits in delayed emesis.

Emend®, a substance P/NK 1-receptor antagonist, represents a new class of anti-emetic agents. Emend was approved in 2004 to be used in combination with other anti-emetic agents for the prevention of acute and delayed CINV in initial and repeat courses of highly emetogenic chemotherapy, including high-dose cisplatin.

The Need Today – Prevention

The prophylaxis of delayed CINV is extremely important in maintaining a patient's quality of life. However, the optimal strategy in dealing with CINV is to prevent both acute and delayed CINV in the initial course of treatment, rather than treating the problem once it has occurred. First, quality of life and patient compliance to further treatment may be maintained if CINV prevention occurs in the initial courses of therapy. In addition, preventing CINV can help to reduce medical cost and the burden of managing CINV. Second, prevention of CINV in the initial course of therapy may lead to reduced CINV in subsequent courses of therapy as experience of CINV with initial courses of chemotherapy is considered to be a risk factor for the development of CINV in subsequent cycles.

Comparison of 5-HT3s

| 5-HT3 | Trade Name | Half-Life | Receptor Binding Affinity pKi (nM) | Routes of Administration |
|--------------|------------|-----------|------------------------------------|--------------------------|
| Dolasetron | Anzemet® | 7.5 | 7.7 | IV & Oral |
| Ondansetron | Zofran® | 4 | 8.1 | IV & Oral |
| Granisetron | Kytril® | 9 | 8.4 | IV & Oral |
| Palonosetron | Aloxi® | 40 | 10.4 | IV only |

Table 1.

Emerging Treatments

| Company Product | Drug | Delivery Technology | Potential Uses | Advantages/Disadvantages |
|--|------------------|--|-----------------------------------|---|
| Abeille Pharmaceuticals (AB-1001) | Granisetron | Transdermal System | Acute & Delayed CINV, RINV & PONV | <ul style="list-style-type: none"> Preventive treatment option that provides protection for the entire 5-day period. Could be easily removed if there is any adverse effect due to therapy. |
| A.P. Pharma (APF530) | Granisetron | Sustained-Release Injectable | Acute & Delayed CINV, RINV & PONV | <ul style="list-style-type: none"> Requires specialist healthcare provider for administration. Requires surgical procedure if removal is necessitated due to any adverse effect from therapy. |
| BDSI, Inc. (Emezine) [®] | Perchlorperazine | Buccal Tablet | Acute CINV, Breakthrough NV? | <ul style="list-style-type: none"> Short duration of action, limited if any, use in delayed emesis. Patient acceptability and taste could present a challenge. |
| Hana Biosciences (Zensana [™]) | Odansetron | Oral Spray Acute | CINV, Breakthrough NV | <ul style="list-style-type: none"> Short duration of action, limited if any, use in delayed emesis. Taste-masking could be a major challenge. |
| ZARS (CHADD + 5-HT3 antagonist) | Granisetron | Controlled Heat-Activated Transdermal System | Acute & Delayed CINV, RINV & PONV | <ul style="list-style-type: none"> Design increases product cost and complexity of administration with no apparent benefits over a simple transdermal system. |

Table 2.

The prevention of CINV may be achieved with the use of risk-assessment models, created from a compilation of data from clinical studies. Risk assessments help to determine which patients are at a higher risk of developing CINV according to patient and treatment characteristics. High-risk patients who are identified through the risk-assessment models may be strictly managed for the prevention of CINV according to specified guidelines. Patients identified at moderate risk for developing CINV may also be treated for the prevention of CINV, while low-risk patients may be spared unnecessary therapy.

The most commonly identified risk factors for developing chemotherapy-induced emesis are: 1) highly emetogenic chemotherapy agents used in treatment; 2) prior CINV; 3) female patients; 4) younger patients; and 5) low alcohol intake.

Emetogenic potential of oncologic agents is classified into 5 levels according to the frequency of emesis without anti-emetic prophylaxis. The moderately and highly emetogenic agents listed further are from the National Comprehensive Cancer Network

(NCCN) guidelines.⁹ Some chemotherapy agents are considered moderately emetogenic at lower doses, and highly emetogenic at higher doses:

Level 1: < 10% frequency of emesis

Level 2: 10% to 30% frequency of emesis

Level 3: 30% to 60% frequency of emesis (amifostine, arsenic trioxide, cyclophosphamide, doxorubicin, epirubicin, hexamethylmelamine, idarubicin, ifosfamide, IL-2, irinotecan, lomustine, methotrexate, mitoxantrone, oxaliplatin)

Level 4: >60% to 90% frequency of emesis (amifostine, busulfan, carboplatin, carmustine, cisplatin, cyclophosphamide, cytarabine, dactinomycin, doxorubicin, epirubicin, melphalan, methotrexate, procarbazine)

Level 5: >90% frequency of emesis (carmustine, cisplatin, cyclophosphamide, dacarbazine, mechlorethamine, streptozocin)

It is important for healthcare providers to properly assess their patients and intended

treatment protocols to determine the risk of their patient developing CINV.¹⁰ Once a patient's risk is determined, healthcare providers should implement prevention protocols according to established guidelines. Quality-of-life assessments have shown that if CINV is uncontrolled, there is: 1) a reduction in scores in cognitive function; 2) insomnia; 3) anorexia; 4) fatigue; 5) dyspnea; and 6) poor overall quality of life.

Additionally, oncology nurses spend an average of approximately 1.5 hours per week on the telephone with their patients at home assessing CINV, indicating that prevention of delayed CINV may allow nurses to have more time to tend to other patients or medical tasks.

Emerging Treatments

What profile would an ideal anti-emetic possess? The consensus is that an ideal anti-emetic would provide: 1) complete control in all settings; 2) no side-effects; 3) convenience and ease of use; 4) fewer drug interactions; 5) a simpler dosing regimen; and 6) no cost barriers to use. Among the several new

products being developed for CINV are drug delivery systems incorporating existing 5-HT3 inhibitors. The most notable of these reformulations, along with their key features are shown in Table 2. It is apparent that a transdermal anti-emetic product comes closest to satisfying the profile of an ideal anti-emetic product. Abeille Pharmaceuticals, Inc., has a transdermal anti-emetic product at an advanced stage of development. Some of the advantages of a transdermal product include: 1) an ideal mode of treatment for cases where the need for the anti-emetic therapy extends beyond 1 day, since the patch will be designed to deliver the drug for up to 5 days; 2) protecting the patient through the completion of, and several hours post, chemotherapy until the patch is removed; 3) maintaining blood levels of the drug in the therapeutic range for the duration of therapy. In addition, the blood levels of the drug will continue in the therapeutic range several hours post removal of the patch; 4) increasing patient confidence in the ability to leave the hospital or the doctor's office after the chemotherapy is administered, knowing that they will not require further intervention for side-effects; 5) improving patient convenience and compliance; 6) removing the need for an oral administration of an anti-emetic during a time period when the patient may not want to ingest anything due to discomfort; 7) helping reduce anticipatory nausea in subsequent chemotherapy treatments; and 8) easily removed by the patient if there is any adverse effect due to the therapy.

A transdermal anti-emetic patch thus represents a major opportunity for a Specialty Pharmaceutical company active in the supportive cancer segment, because in addition to CINV, there exist significant opportunities in radiation-induced nausea and vomiting (RINV) and in post-operative nausea and vomiting (PONV). ■

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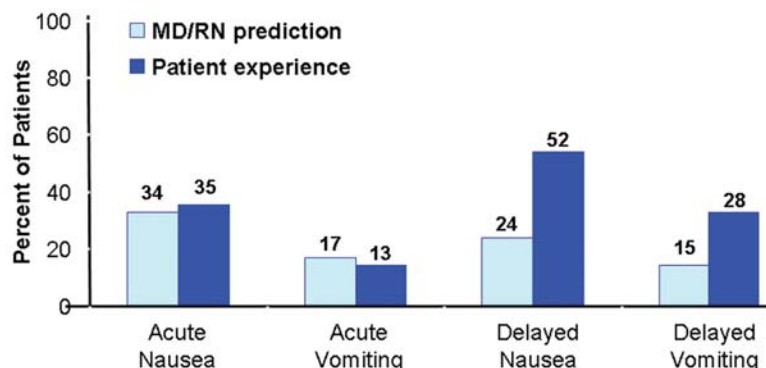
Mr. Suresh Borsadia has more than 14 years experience in the pharmaceutical and drug delivery industries, with expertise and experience in R&D and business/corporate development activities. Mr. Borsadia has a demonstrated record of successfully managing multiple projects and building R&D organizations in early stage companies. Prior to founding Abeille Pharmaceuticals, Inc., he was with Lavipharm for 7 years, where he played a leading role in the company's R&D, in-licensing, and out-licensing activities. He was part of the Senior Management team involved in M&A and fundraising activities. Prior to that, he worked at two other leading drug delivery companies, TheraTech, Inc., (now Watson Pharmaceuticals), and Bertek, Inc., (now Mylan Technologies, a Division of Mylan Labs.). His professional background is in Pharmacy & Pharmaceuticals.



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Dr. Kalpana Patel has more than 12 years of experience in the pharmaceutical industry and has led preformulation, formulation, process development, and validation initiatives for a range of Rx, Rx to OTC switches, OTC products, and medical devices. Dr. Patel most recently was the Pipeline Development Director for Johnson & Johnson Consumer Companies. During her tenure at J&J, she held leadership responsibilities involving product development, life cycle management, and was involved in advisory meetings with thought leaders. In addition, she was actively involved in interaction with global regulatory bodies. While at J&J, she also founded the Johnson & Johnson community of product/process development.



Physicians and nurses from 14 oncology practices in 6 countries
Patients: 75% women; 78% Mod emetic chemo; 50% breast cancer; 18% lung cancer
S. Grunberg, et.al. (2004). *Cancer*, 100, 261-268.

Figure 2. Perceptions & Reality - Moderately Emetic Chemotherapy.