



## PALLIATIVE CARE CASE OF THE MONTH

### “Second-Line Anti-emetic Therapies for Refractory Chemotherapy-Induced Nausea and Vomiting”

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**Case:** Ms. ML is a 27-year-old woman with recently diagnosed ovarian cancer after presenting to the ED with worsening abdominal pain. CT imaging showed a 4cm cystic mass extending from her right ovary, and the surgical pathology revealed ovarian adenocarcinoma. Two weeks post-operatively, ML was hospitalized for initiation of chemotherapy, and the palliative care service was consulted for symptom management. Despite having received treatment with ondansetron, aprepitant, dexamethasone, lorazepam, and haloperidol, she developed significant nausea and vomiting on the first day of chemotherapy infusion with symptoms worsening on her second day of chemotherapy. ML described feeling utterly miserable and fearful about her next chemotherapy infusion, and she was continuing to experience nausea and repeated episodes of emesis overnight with minimal oral intake. ML also described an underlying history of anxiety disorder predating her cancer diagnosis. At home she typically smoked marijuana on a daily basis to help manage her anxiety symptoms, which she reported did not interfere with her successful function at work and school. On review of systems, ML noted she had abdominal discomfort for which she was taking low dose oxycodone and that she had not moved her bowels for several days.

**Discussion:** Nausea and vomiting (NV) are commonly reported side effects with chemotherapy.<sup>1</sup> The primary pathway for NV involves the chemotherapy drugs directly stimulating the chemoreceptor trigger zone (CTZ), in the area postrema at the base of the fourth ventricle. Activated receptors in the CTZ transmit signals to the vomiting center in the brainstem to produce NV. Receptors in the CTZ include serotonergic receptor 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>), dopaminergic (D<sub>2</sub>) and neurokinin type 1 (NK-1) receptors. In addition, chemotherapy can damage GI mucosa causing local release of 5HT<sub>3</sub> neurotransmitters by gut enterochromaffin cells, activating peripheral pathways along the vagus and splanchnic nerves and directly triggering the vomiting center. Finally, chemotherapy-associated anxiety may also stimulate the vomiting center through central cortical pathways. Whether transmitted via signals from the CTZ, the cortex, or peripheral inputs, the vomiting center has several different receptors involved in initiating the vomiting reflex: muscarinic acetylcholine (ACh), histamine type 1 (H<sub>1</sub>), and 5-hydroxytryptamine type 2 (5-HT<sub>2</sub>).<sup>1</sup>

Given the pathways for chemotherapy-induced nausea and vomiting described above, 5-HT<sub>3</sub> and NK-1 receptor antagonists such as ondansetron and aprepitant, in combination with dopamine antagonists such as haloperidol, are typically effective for treatment of NV. In some cases, however, patients may develop breakthrough nausea and vomiting despite adequate standard therapy requiring additional or alternative anti-emetic medications. According to guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network, there are several categories of second-line agents that may be useful in refractory cases.<sup>2,3</sup> The cannabinoids dronabinol and nabilone are both FDA approved for refractory chemotherapy-induced nausea and vomiting.<sup>4</sup> Unlike other anti-emetic medications which block receptor activity for their therapeutic effect, cannabinoid effect is exerted by agonist activity on the cannabinoid receptor in the brain CB<sub>1</sub>.<sup>5</sup> Dronabinol (trade name Marinol) is a Schedule 3 synthetic THC (delta-9 tetrahydrocannabinol). Starting dose is typically 5mg 2 hours prior to chemotherapy and every 4 hours as needed, with a maximum dose of 15mg. Nabilone (Cesamet) is a Schedule 2 drug with longer onset and duration of action, and is dosed 1-2 mg twice or three times daily as needed. Studies demonstrate that dronabinol and nabilone are effective for treatment of nausea and vomiting; however, their use is limited by their side effect profile including vertigo, xerostomia, hypotension, dysphoria, and hallucinations.<sup>4,5</sup> Olanzapine is an atypical antipsychotic which antagonizes multiple neurotransmitters including dopamine at D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> brain receptors; acetylcholine at muscarinic receptors; serotonin at 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>6</sub> receptors; catecholamines at alpha-1 adrenergic receptors; and histamine at H<sub>1</sub> receptors.<sup>6</sup> Several studies have demonstrated its utility for treating chemotherapy-induced nausea and vomiting.<sup>6</sup> No studies have specifically compared it to haloperidol or other atypical anti-psychotics for treatment of nausea, although several authors have argued that it is the multiplicity of olanzapine's receptor activity which contributes to its effectiveness. The recommended dosing is 5mg orally daily starting 1-2 days before chemotherapy, then 5-10mg daily for days 1-4 of chemotherapy. Side effects include sedation, dry mouth, increased appetite, hyperglycemia and postural hypotension.<sup>2,3</sup> Metoclopramide has central and peripheral anti-dopaminergic activity, and at high doses also exerts 5-HT<sub>3</sub> antagonist effect which is thought to contribute to its anti-emetic effect.<sup>1,2</sup>

*Personal details in the case published have been altered to protect patient privacy.*

For palliative care consultations please contact the Palliative Care Program at PUH/MUH, 647-7243, beeper 8511, Shadyside Dept. of Medical Ethics and Palliative Care, beeper 412-647-7243 pager # 8513, Perioperative/ Trauma Pain 647-7243, beeper 7246, UPCI Cancer Pain Service, beeper 644-1724, Interventional Pain 784-4000, Magee Women's Hospital, beeper 412-647-7243 pager #: 8510, VA Palliative Care Program, 688-6178, beeper 296. Hillman Outpatient: 412-692-4724. For ethics consultations at UPMC Presbyterian-Montefiore and Children's page 958-3844. With comments about "Case of the Month" call Dr. Robert Arnold at (412) 692-4834.



**(Discussion Continued)**

Because of its low therapeutic index, metoclopramide is typically reserved for patients who are intolerant or refractory to first line anti-serotonergic agents. Dosing is 10-40 mg IV 30 minutes prior to chemotherapy, then every 4 to 6 hours as needed.<sup>3</sup> An alternate dosing strategy is 1-2 mg/kg 30 minutes before chemotherapy and then repeated 2 hours after chemotherapy for 2 doses, and then every 3 hours for 3 doses. Side effects include dystonia, akathisia, sedation, and esophageal spasm. Pretreatment with diphenhydramine will decrease risk of extrapyramidal reactions.<sup>2</sup>

Benzodiazepines are most useful in cases of anticipatory NV, which is thought to be a conditioned reflex as a result of prior poor control of emesis during chemotherapy treatment.<sup>3</sup> The phenomenon involves the development of NV when a sensory stimulus (ie, the sights, sounds, or smells of chemotherapy clinic) becomes paired with the experience of symptomatic chemotherapy treatment. After a conditioning period (ie, repeated chemotherapy infusions in clinic), the sensory stimulus or anxiety from negative anticipation may trigger NV before the patient has even received the chemotherapy infusion.<sup>7</sup> The mechanism involves signals along intracerebral projections in the cortex directly stimulating the vomiting center. Older studies had described the phenomenon in up to 25% of patients with poorly controlled symptoms by the fourth treatment cycle; however, the frequency appears to have decreased with the advent of more effective anti-emetic regimens. Patients with refractory NV are at higher risk of developing anticipatory NV. The intermediate-acting benzodiazepine lorazepam is helpful for treatment of anticipatory NV and as an adjunct in cases of refractory NV, with starting doses of 0.5-1mg oral or IV, and up to 2mg, every 6-8 hours as needed for anxiety and nausea.<sup>7</sup>

**Resolution of the Case:** Based on her symptoms and previous history, Ms. ML was started on dronabinol 5mg three times daily during her chemotherapy treatment while in the hospital, along with the scheduled ondansetron and haloperidol. A bowel regimen of senna and miralax was also initiated, as opioid-induced constipation was likely contributing to her symptoms. Within 24 hours, ML had resolution of emesis and improvement of her nausea, enabling her to resume oral intake.

**Summary:** While standard anti-emetic therapies with 5-HT<sub>3</sub> and dopamine antagonists are effective and well-tolerated in most cases of chemotherapy-induced nausea and vomiting, occasionally refractory symptoms necessitate addition of a second-line agent such as a cannabinoid, olanzapine, or metoclopramide. Patient characteristics such as age, previous experience with cannabinoids, and medical comorbidities will impact the choice of second-line agent. Dronabinol or nabilone may be most effective in younger patients and those with previous experience of tolerating cannabinoids. Olanzapine is preferable in elderly patients or populations for whom there may be a concern about the psychoactive properties of cannabinoids. Substitution of high dose IV metoclopramide for other dopaminergic and 5-HT<sub>3</sub> medications could also be helpful in certain cases, especially if there are additional concerns about GI dysmotility or intolerance to standard 5-HT<sub>3</sub> agents.

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