EMESIS DURING CHEMOTHERAPY: A REVIEW ON GRANISETRON, ITS EFFICACY AND DELIVERY SYSTEMS

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ABSTRACT
Nausea and vomiting are common problems occurs in disease, non-disease condition and after the chemotherapy, results from the activation of protective physiological mechanism in order to eliminate the toxin from the body. Principal four pathways that act on vomiting center to trigger nausea and vomiting are chemotherapy trigger zone (CTZ), cortex, peripheral pathway and the vestibular system. In emesis different treatment strategy are used in which Granisetron is a drug emerge as a drug of great potential to overcome chemotherapy induce nausea and vomiting. Current review aims to introduce emesis (CIE) during chemotherapy along with different novel therapeutic approaches and various clinical studies. In variety of studies to overcome the CIE novel approaches are of great importance.

Keywords: Emesis, Granisetron delivery system, Chemotherapy.

INTRODUCTION
Vomiting is medically known as “EMESIS”. It is a forceful expulsion of the contents of one’s stomach through the mouth and sometimes the nose. The feeling of about vomiting is called as nausea, which occurs as a precedes, but not always leads to vomiting [1]. Vomiting is a complicated process and includes a pre-ejection phase, ejection phase and post-ejection phase. In pre-ejection phase gastric smooth muscle relaxes and retrograde peristalsis. In ejection phase abdominal and diaphragmatic muscles contract [2]. In post-ejection phase come back to quiescent state [3].

There are 4 pathways that which originates the vomiting center to trigger nausea and vomiting i.e. chemotherapy trigger zone (CTZ), cortex, peripheral pathway and the vestibular system. The CTZ is exterior to blood brain barrier and reveal to toxins, i.e. chemotherapy and cerebral spinal fluid which triggers vomiting. In CTZ DA, 5HT, NK1 neuro receptors are present. Dopamine receptor antagonists act in the neural pathway. Clozapine was the first typical antipsychotic. Antipsychotic are known to be used for nausea and vomiting. They act by obstruct the dopamine receptors which are class of metabotropic G protein-coupled receptors that are prominent in the vertebrate central nervous system. The neurotransmitter dopamine is the main endogenous ligand for dopamine receptors [4].

Chemotherapy induced nausea and vomiting
Nausea and vomiting are the two most panic factors of chemotherapy. Various other causes of nausea and vomiting that are linked with cancer or other treatments for example treatment with radiation block in the intestine caused by the tumor, reaction of medications, imbalance in body fluids [5].


Classification of chemotherapy induced nausea and vomiting [7].
1. Acute CINV: It is the phenomena that occur in the first 24 h when patients received chemotherapy.
2. Delayed CINV: It is the phenomena that occur more than 24 h when patients received chemotherapy.
3. Anticipatory CINV: It is a learned response which occurs after patients CINV had poor controlled in the past.

Fig. 1: Natural mechanism of controlling nausea and vomiting

Fig. 2: Percentage pervalence of emesis in cancer patients undergoing chemotherapy

Fig. 3: Three types of chemotherapy induced nausea and vomiting: Timing and treatment
This diagram shows that line going along with the arrow on it told that Day 1, Day 0, Day 1, Day 2, is usually chemotherapy. Chemotherapy is given on Day 0 in this anticipatory happen any time up until then. Acute is generally on the first day of treatment and then delayed is mentioned from Day 1 onward.

**General risk factors and etiologies**

Not all the cancer patients familiar the nausea and vomiting. [9] Several patient characteristics have also been identified. Includes the following points:

1. Occurrence and seriousness of nausea and vomiting during past courses of chemotherapy [10].
3. Age: Nausea and vomiting more likely to be in younger patients than 50 y old [12].

**Table 1: Grading methods for adverse events of nausea and vomiting: national cancer institute’s [8]**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1</td>
<td>Loss of appetite without alteration in eating habits</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Oral intake decreased without significant weight loss, dehydration or malnutrition.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Inadequate oral caloric or fluid intake, tube feeding</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Grade not available</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Grade not available</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1-2 episodes (separated by 5 min) in 24 h</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3-5 episodes (separated by 5 min) in 24 h</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt; Episodes (separated by 5 min) in 24 h; tube feeding, TPN</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Life threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

N& V= Nausea and vomiting (emesis); TPN= Total parenteral nutrition, a Adapted from National Cancer Institute (CTCEA version 4.0 2010), b Definition: A disorder identify by a queasy sensation and/or the urge to vomit, c Definition: A disorder identify by the reflexive act of ejecting the contents of the stomach through the mouth.

**Table 2: Emetogenic risk-related with Interavenously (iv) administered Antineoplasticagents [15]**

<table>
<thead>
<tr>
<th>Level</th>
<th>Grade</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Minimal risk,&lt;10%</td>
<td>Vinblastin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Level 2</td>
<td>LOW RISK, 10-30%</td>
<td>Fluorouracil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topotecan</td>
</tr>
<tr>
<td>Level 3</td>
<td>Moderate risk, 31-90%</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboptatin</td>
</tr>
<tr>
<td>Level 4</td>
<td>HIGH RISK,&gt;90%</td>
<td>Cisplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclophosphamide</td>
</tr>
</tbody>
</table>

The chemotherapy trigger zone (CTZ) is the region located in the area postrema and the nucleus solitaries (NTS) are the important relay areas for afferent impulses arising in the g. i. t throat and other viscera (KD Triphathi). The CTZ is having high level concentration of serotonin (5-HT3), dopamine (D2), and opioid receptors and the NTS is luxury in enkephaline, histamine and cholinergic receptors and 5-HT3 receptors [16].

**5-HT3 Antagonists**

It is a class of drug that work as receptor antagonists at 5-HT3 receptor, a scientific serotonin receptor found in the terminals of vagus nerve and various areas of the brain [17].

**5-HT3 Receptor**

It is a member of the superfamily of the ligand-gated ion channels; it also includes the neuronal nicotinic acetylcholine receptors (nAChRs) and inhibitory neurotransmitter receptors for GABA and glycine.

It consists of 5 subunits arranged around a central ion conducting pore, which is permeable to sodium, potassium and calcium ions [19].

**Receptors involved in various causes of nausea and vomiting [20].**

**Causes of nausea and vomiting Receptors involved**

1. Cancer chemotherapy
2. Infection/inflammation
3. Vestibular system dysfunction
Anti-Emetic

It is a drug that is powerful towards vomiting and nausea. There are generally used to treat motion sickness and the side effects of opioid analgesics, general anesthetics and chemotherapy administered against cancer [21].

Dopamine antagonists vanquish pro-emetic stimuli by blocking D2 receptors in the chemoreceptor trigger zone (CTZ).

5-HT3 antagonists have been more recently progress to block the nausea and vomiting reflexes mediated by stimulation of 5-HT3 receptors in both the small intestine and the CTZ.

Antihistamines, has widely being used in the migraine and generally used for motion sickness as they work at the level of the vestibular apparatus. Anticholinergic agents i.e. atropine and hyoscine are quite unsuccessful in the treatment of prevention of vomiting due to causes other than motion [22].

![Fig. 4: Certain different sites of action of anti-emetics](image)

<table>
<thead>
<tr>
<th>Table 3: Classification of 5-HT3 receptor antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
</tr>
<tr>
<td>Trade Name</td>
</tr>
<tr>
<td>Half-Life</td>
</tr>
<tr>
<td>Receptor Binding Affinity Pki(nM)</td>
</tr>
<tr>
<td>Route of Administration</td>
</tr>
</tbody>
</table>

Drug; granisetron; Granisetron is a potent serotonin 5-HT3 receptor antagonist used as an antiemetic to treat nausea and vomiting following chemotherapy. Common adverse events related with granisetron [23].

1. Constipation.
2. Diarrhea.
3. Asthenia.
4. Somnolence.
5. Headache.
6. Anemia
7. Infertility.

**Structure of granisetron**

![Chemical formula: C<sub>18</sub>H<sub>24</sub>N<sub>4</sub>O, Mol mass: 312.41 gm/mol](image)

**Pharmacokinetic profile**

1. Bioavailability: 60%.
2. Protein binding: 65%.
3. Half-life: 3-14 h.
4. $\log P$: 2.64.
5. $\log P K_{i}$ 9-14.7) not suitable for intestinal absorption,
7. Dose: 1-2 mg

**Mechanism of action of granisetron**

It is a selective 5-hydroxytryptamine3 (5-HT3) receptor antagonist with little or no affinity for other serotonin receptors including 5-HT1, 5-HT1A, 5-HT1B/C, and 5-HT2 or alpha 1 or alpha 2 or $\beta$-adrenoreceptors for dopamine D2, histamine H1.

Serotonin receptors of the 5-HT3 type are located peripherally on vagal nerve terminal and centrally in the CTZ of the area postrema. During chemotherapy–induced vomiting, mucosal entero chromaffin cells, release serotonin, which stimulates 5-HT3 receptors.
Fig. 5: Site of action of 5HT3 receptor antagonists

Table 4: Formulation of granisetron approved by FDA

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation</th>
<th>Invention</th>
<th>Year Approval</th>
<th>Approved Agency</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Transdermal patch</td>
<td>SANCUSO (KYTRIL)</td>
<td>2008</td>
<td>FDA</td>
<td>Prostrakan</td>
</tr>
<tr>
<td>2.</td>
<td>Granisetron HCl injection USP</td>
<td>KYTRIL® Injection</td>
<td>1993</td>
<td>FDA</td>
<td>PARENTA Pharmaceutical</td>
</tr>
<tr>
<td>3.</td>
<td>Granisetron tablets</td>
<td>Kytril tablets</td>
<td>1995</td>
<td>FDA</td>
<td>Roxane Laboratories</td>
</tr>
</tbody>
</table>

Table 4: Advantage and disadvantage of various formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Transdermal patch.</td>
<td>1. Provides a controlled release of medication. 2. Easy to apply.</td>
<td>1. Medications whose molecules are small enough to penetrate the skin can be delivered by this method.</td>
<td>[25]</td>
</tr>
<tr>
<td>3. Oral disintegration tablets.</td>
<td>1. Easy to administer geriatric, pediatric, mentally disabled, who cannot swallowed the tablet. 2. The bioavailability is greater.</td>
<td>1. The ODT's size for both easy to swallow and easy to handle is difficult to achieve. 2. Expensive.</td>
<td>[26]</td>
</tr>
<tr>
<td>4. Injectables</td>
<td>1. Bypasses the digestive system. 2. More efficient usage.</td>
<td>1. Increased chance of infection. 2. Increased chance of infection.</td>
<td>[27]</td>
</tr>
</tbody>
</table>

Problems associated with the conventional dosage form

Conventional dosage form i.e. tablets or capsules are recent facing problems such as dysphagia, which follow high incidence of non-compliance and making the therapy inadequate [28]. Problems associated with conventional oral dosage forms involve the mentally ill, the developmentally disabled, and patients who are uncooperative on taking less liquid-intake plans or are nauseated [29].

Challenges for development for novel formulation

1. The solubility landscape.
2. Low "hit" rate for novel drugs.
3. Increasing quality-Q &B.
4. Reducing the cost base.
Various novel formulation of granisetron

1. Bilayer buccal tablets of granisetron.
2. Transdermal patches of granisetron.

3. A nanoemulsion of granisetron.

In the field of formulating the granisetron dosage form a number of approaches including fast dissolving tablets, nanoemulsions, transdermal patch, bilayer buccal tablets etc have come in to play which is represented in table: 5,6,7,8.

Table 4: table showing problem regarding formulation and improvement in the formulation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Problem regarding formulation</th>
<th>Improvement</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fast dissolving tablets.</td>
<td>1. Unpleasant taste [30]</td>
<td>Taste masking in FDTs is attained by adding sweet–tasking substances such as diluents, adding flavors or encapsulating the unpleasant drug into micro particles or granules.</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>2. Not enough mechanical strength.</td>
<td>Wow tab and durasolv Technologies can make tablets that are importantly hard and durable to allow them to be packed in multi-dose bottles.</td>
<td>[32]</td>
</tr>
<tr>
<td>2. Effervescent granules.</td>
<td>Instability in presence of moisture, problem in packing and storage. [33]</td>
<td>Stability of effervescent granules and powder is significantly enhanced by their packing in aluminum bags tightly closed.</td>
<td>[34]</td>
</tr>
<tr>
<td>3. Film coated tablets.</td>
<td>Film cracking [35]</td>
<td>PVA-PEG based polymer is successful in attaining the reduced process time and energy consumption, for the production of pharmaceutical formulations.</td>
<td>[36]</td>
</tr>
<tr>
<td>4. Injections</td>
<td>Pain [37]</td>
<td>Micro emulsion is a recent approach which has potential to reduce the pain on injection.</td>
<td>[38]</td>
</tr>
</tbody>
</table>

Table 5: Fast dissolving tablet of granisetron

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients used</th>
<th>Conclusion</th>
<th>Formulation type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sodium starch glycolate cross povidone, mannitol, microcrystalline cellulose, sodium stearyl fumerate, granisetronHCl.</td>
<td>Drug release (10w, 20 min)</td>
<td>Design of fast dissolving granisetronHCl tablets using novel co-processed superdisintegrants.</td>
<td>[39]</td>
</tr>
<tr>
<td>2.</td>
<td>GranisetronHCl, sodium bicarbonate, citric acid, tartaric acid, aspartame, flavor, talc, mannitol, sodium stearyl fumerate, croscarmellose sodium.</td>
<td>In-vitro dispersion time of 10 sec of formulation</td>
<td>Formulation design of fast dissolving tablet of granisetron using effervescent blend with improved efficacy.</td>
<td>[40]</td>
</tr>
</tbody>
</table>

Table 6: Nanoemulsion of granisetron

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients used</th>
<th>Conclusion</th>
<th>Formulation type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Granisetron, Lipoid E80, HPMC, HP-β-CD, tween80, sodium taurocholate, lauroglycol90, poloxamer188, penicillin, streptomycin.</td>
<td>Size of oil droplet was 50 nm.</td>
<td>A novel lipid nanoemulsion system for improved permeation of granisetron.</td>
<td>[41]</td>
</tr>
<tr>
<td>2.</td>
<td>GranisetronHCl, isopropylmyristate, n-methylpyrrolidone, tween85, ethanol, methanol.</td>
<td>No changes in long term stability and accelerating stability studies. 12 mo stable at room temperature.</td>
<td>Preparation and the in-vitro evaluation of nanoemulsion system for the transdermal delivery of granisetronHCl.</td>
<td>[42]</td>
</tr>
</tbody>
</table>

Table 7: Bilayer buccal tablet of granisetron

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients used</th>
<th>Conclusion</th>
<th>Formulation used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Granisetron, sodium alginate, HPMC 50cps, carbopol 934p, polyvinylpyrrolidine K-30, polyethylene glycol400,ethylcellulose, D-mannitol.</td>
<td>Final formulation having composition 5A (47% W/W), CP (3%)W/W), PVP (3%)W/W) and DM (15%)W/W) was found to be promising having in-vitro drug release of 94% in 8h along with bioadhesion strength (4.6g).</td>
<td>Formulation design and evaluation of bilayer buccal tablets of granisetronHCl.</td>
<td>[43]</td>
</tr>
<tr>
<td>2.</td>
<td>GranisetronHCl, sodium carbomethylcellulose, HPMC15cps, carbopol 934p, ethylcellulose, aspartame, magnesium stearate, D-mannitol.</td>
<td>Final formulation having composition HPMC cps (47% W/W), Carbopol 934p (3%)W/W) and mannitol (45%)W/W), was found to be promising having in-vitro release of 94% in 8h along with bioadhesion strength (4.3 gm).</td>
<td>Design and evaluation of buccoadhesive bilayer tablets of granisetronHCl.</td>
<td>[44]</td>
</tr>
</tbody>
</table>
and curing patients could not proceed until the parallel development of combination chemotherapy regimens capable of prolonging lives and reducing side effects in cancer treatment, development of effective strategies. Various combinations of granisetron with other drugs and granisetron alone are used in chemotherapy for the treatment of emesis. Table: 9 indicate the usage of granisetron in various clinical studies thus conforming its efficacy and safety status.

**Table 8: Transdermal patch of granisetron**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients used</th>
<th>Conclusion</th>
<th>Formulation used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>GranisetronHCl, Lutrol F-127, potassium dihydrogen phosphate, sodium hydroxide, silver chloride, silver wire.</td>
<td>It showed that the feasibility of granisetron transdermal patch transport through Lutrol F-127 gel by iontophoresis.</td>
<td>Enhanced transdermal delivery of granisetron by using iontophoresis.</td>
<td>[45]</td>
</tr>
<tr>
<td>2.</td>
<td>Crystalline granisetronHCl, amorphous granisetron patch, placebo patch, silicon low background sample holder.</td>
<td>Simpler and better technique for the crystallinity determination in transdermal patch.</td>
<td>An approach to determine crystalline content of granisetron in transdermal patches using X-ray diffraction technique.</td>
<td>[46]</td>
</tr>
</tbody>
</table>

**Therapeutic use**

The granisetron serves as an important therapeutic candidate in treating emesis during chemotherapy treatment. Now a day's various combinations of granisetron with other drugs and granisetron alone are used in chemotherapy for the treatment of emesis. Table: 9 indicate the usage of granisetron in various clinical studies thus conforming its efficacy and safety status.

**Table 9: Clinical studies (Comparative studies)**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Studies</th>
<th>Reference</th>
<th>Result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Efficacy and tolerability of transdermal granisetron vs. control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double blind, phase III study.</td>
<td>[47]</td>
<td>In granisetron transdermal delivery system group headache is 0.3% which is lower as compared to oral granisetron group i.e. 2.5% but constipation was more frequent in GTDS i.e. 6.6% as compared to oral granisetron i.e. 3.1%.</td>
<td>The study indicates the GTDS (Granisetron transdermal delivery system) is well tolerated in cancer patients.</td>
</tr>
<tr>
<td>2.</td>
<td>Granisetron versus Dexamethasone in prophylaxis of nausea and vomiting after laparoscopic cholecystectomy.</td>
<td>[48]</td>
<td>In the first 24 h after operation, 7 patients in the dexamethasone group had nausea and 3 patients having vomiting. In granisetron group 5 patients had nausea and 2 have vomiting and there is no difference between the groups. In one case dexamethasone shows headache and in granisetron group one case show vertigo and one case headache. No difference in 2 groups in the regard (Pvalue: 0.614).</td>
<td>Concludes that dexamethasone and granisetron injection before anesthesia induction has same effects on nausea and vomiting prophylaxis after laparoscopic Cholecystectomy.</td>
</tr>
<tr>
<td>3.</td>
<td>Efficacy of generic granisetron vs. kytril for PONV in major gynecological operations: a randomized, double blind clinical trial.</td>
<td>[49]</td>
<td>In generic granisetron group there were 47 and 13 patients and in kytril group 45 and 15 patients experience hysterectomy and myomectomy. No dissimilarity between two treatment groups concerning postoperative nausea and vomiting control during 18 h after drugs administration.</td>
<td>Generic granisetron utilize efficacy against PONV after gynaecological surgeries which is non-inferior to that of kytril.</td>
</tr>
<tr>
<td>4.</td>
<td>Pre-treatment with intravenous granisetron to alleviate pain on propofol injection: a double blind, randomized, controlled trial.</td>
<td>[50]</td>
<td>In the second day of chemotherapy in ondansetron and it was only 3.3% in granisetron group due to adverse effects of antiemetic drug itself (p=0.001). Extremely experience of vomiting were found on the second day in ondansetron group 33.3% and in granisetron group 3.3% (P=0.003). Though adverse effects like headache, constipation, abdominal pain and loose motions were reported in both group of children but there were less in children who receive granisetron. On the second day of therapy nausea and vomiting wax maximum in ondansetron and less in granisetron. On day 4 results was significant.</td>
<td>They conclude that pre-treatment with granisetron along with venous occlusion for 1 min for prevention of propofol-induced pain was highly successful.</td>
</tr>
<tr>
<td>5.</td>
<td>Ondansetron versus granisetron in the prevention of chemotherapy induced nausea and vomiting in children with acute lymphoblastic leukemia.</td>
<td>[51]</td>
<td>About 36.7% patients had experience of nausea on day four of chemotherapy in ondansetron and it was only 3.3% in granisetron group due to adverse effects of antiemetic drug itself (p=0.001). Extremely experience of vomiting were found on the second day in ondansetron group 33.3% and in granisetron group 3.3% (P=0.003). Though adverse effects like headache, constipation, abdominal pain and loose motions were reported in both group of children but there were less in children who receive granisetron. On the second day of therapy nausea and vomiting wax maximum in ondansetron and less in granisetron. On day 4 results was significant.</td>
<td>Conclude that to prevent acute and delayed chemotherapy induced and vomiting in children with all, oral granisetron is more effective as well as well tolerated with less adverse effect as compared to ondansetron.</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Nausea and vomiting in cancer chemotherapy are highly distressing side effects in cancer treatment, development of effective combination chemotherapy regimens capable of prolonging lives and curing patients could not proceed until the parallel development of highly effective, innovative CINV prevention and treatment strategies. Among different treatment approaches the novel vesicular and particulate carrier are seems to be of great importance and have huge applications because of their targeting potential to act at...
molecular basis and better control over tumor, restricted bio-
distribution of drug as compare to conventional formulation. In
various clinical studies 5-HT3 antagonist more specifically
granisetron and ondansetron was found to be of great importance in
management of CINV but common adverse events include mild
headache, transient elevation of hepatic aminotransferase levels,
and constipation, however older 5-HT3 antagonists (e. g.,
granisetron, ondansetron), have shown lower efficacy for the
delayed type of chemotherapy-induced nausea and vomiting
compared with the acute type, other category of drug neurokinin-1
(NK1) receptor antagonists aprepitant and fosaprepitant, and
glucocorticoids were also effective to CINV.

CONFLICT OF INTERESTS
Declared None

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