Preface

This guide will provide a broad summary of chemotherapy-induced nausea and vomiting, its classification, and risk factors, and focus mainly upon its pathophysiology. The guide is not meant to be comprehensive. Before application of any practice or therapy mentioned here, patients should be thoroughly informed of any potential risks versus the possible benefits. Please refer to the *Prevention of Nausea and Vomiting in Cancer Patients* for further information.

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Pathophysiology of Chemotherapy-induced Nausea and Vomiting

Derived from the
Prevention of Nausea and Vomiting in Cancer Patients
by Matti Aapro, Karin Jordan, Petra Feyer

Springer Healthcare

Education

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Introduction

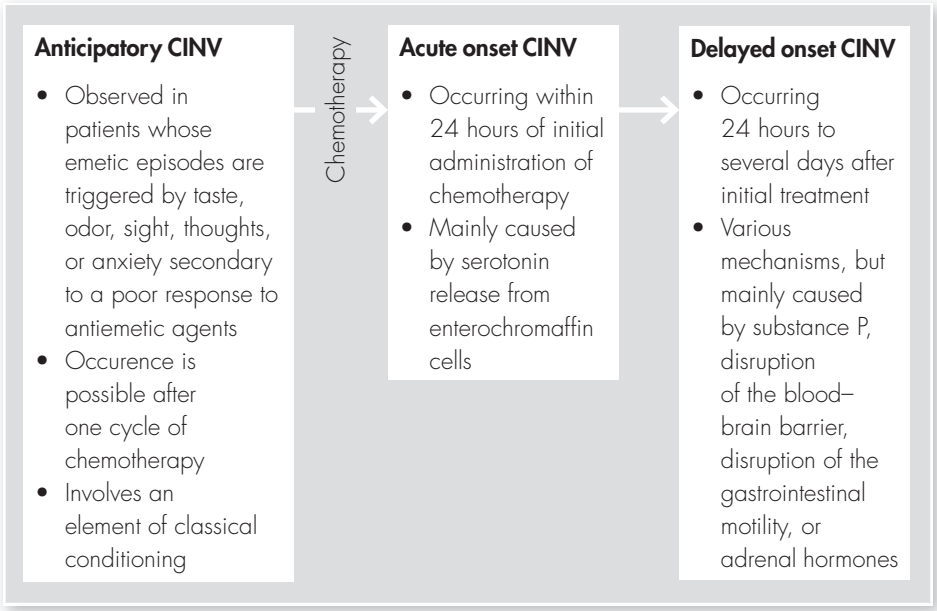
Patients with cancer may experience many side effects while receiving chemotherapy, but few side effects are more feared than nausea and vomiting (see table below) [1,2]. In the past, nausea and vomiting were inevitable side effects of chemotherapy and forced up to 20% of patients to postpone or refuse potentially curative treatment [3]. However, clinical research since the late 1980s has led to steady improvements in the control of chemotherapy-induced nausea and vomiting (CINV) for patients with cancer.

Rank	1980s	1990s	2000s
1	**Vomiting**	Alopecia	**Nausea/vomiting**
2	**Nausea**	**Nausea**	Diarrhea
3	Alopecia	Tiredness	Peripheral neuropathy
4	Anticipation of treatment	Anticipation of treatment	Hand–foot syndrome
5	Length of treatment in clinic	Depression	Mucositis

Patient perception of the side effects of cancer chemotherapy. Adapted from Coates et al [1], Griffin et al [2], and Kuchuk et al [4].

Classification

CINV can be classified into the following categories [3,5,6]:



Risk factors

The main risk factor associated with CINV is the emetogenic potential of the chemotherapy agent used, but individual characteristics of the patient should also be taken into consideration and can vary substantially from patient to patient.

Emetogenic potential

The emetogenic potential of a chemotherapy agent is the most important risk factor for determining the degree of CINV, and is classified into four risk groups [7,8]:

High risk (>90%)	Acute emesis ++	Delayed emesis ++
Moderate risk (30–90%)	Acute emesis ++	Delayed emesis +
Low risk (10–30%)	Acute emesis +	Delayed emesis –
Minimal risk (<10%)	Acute emesis –	Delayed emesis –

The emetogenic potential of a chemotherapeutic agent varies according to the specific drug used, ranging from cisplatin, dacarbazine, or cyclophosphamide, which may cause severe vomiting, to vinca alkaloids or bevacizumab, which may cause minimal emesis.

Different intensities of emesis can depend on the administration of the drug – for example, a drug administered via bolus injection can cause severe emesis compared to the same drug administered in a continuous infusion. This is due to higher levels of in vivo drug concentration being present over short time application.

Patient risk factors

Various patient characteristics should be taken into account when determining the risk of developing CINV. These features are listed below with subsequent descriptions. The characteristics of affected patients suggest a large group of factors that can, each by itself or in combination, modulate the occurrence of CINV.

Previous experience of poorly controlled emesis
Patients with previous CINV experiences are more likely to develop CINV in response to new chemotherapy treatments.
The degree of side effects that were previously experienced is important. If emetic control was sufficient during previous chemotherapy, the percentage of patients who do not experience emesis in subsequent chemotherapy courses is larger than it is for patients who had insufficient previous antiemetic treatment [9].
Sex and age
Sex is arguably one of the most important prognostic factors of CINV; females are more predisposed to CINV than males.
Age is also an important risk factor, as younger patients (<50 years) experience more severe CINV than older patients (>65 years).

Alcohol intake

Studies have suggested that a history of chronic heavy alcohol abuse (>100 g/day) may be associated with better control of CINV [9,10]. It has been assumed that chronic alcohol exposure results in a decreased sensitivity of the chemoreceptor trigger zone, but knowledge of this area is still incomplete.

However, it is of note that a low alcohol intake on a regular basis is associated with a lower control of CINV.

History of motion sickness

Patients susceptible to motion sickness report a greater frequency, severity, and duration of CINV following treatment.

Increases risk of CINV

- Experience of nausea and/or vomiting during previous chemotherapy
- Age <50 years
- Female gender
- Anxiety
- Pretreatment nausea
- Fatigue
- Chemotherapy as an outpatient
- Low intake of alcohol
- Impaired quality of life
- History of motion sickness
- Pain
- Vomiting during pregnancy

Decreases risk of CINV

- Chemotherapy as an inpatient
- Severe alcohol consumption

Overview of patient characteristics that influence the occurrence of CINV. Adapted from Hesketh [11], Jordan et al [12], and Morrow et al [13].

Pathophysiology

The pathophysiology of CINV is not entirely understood; however, it is thought to have many contributing pathways. The general mechanisms involved in this highly complex reflex are summarized in the following sections.

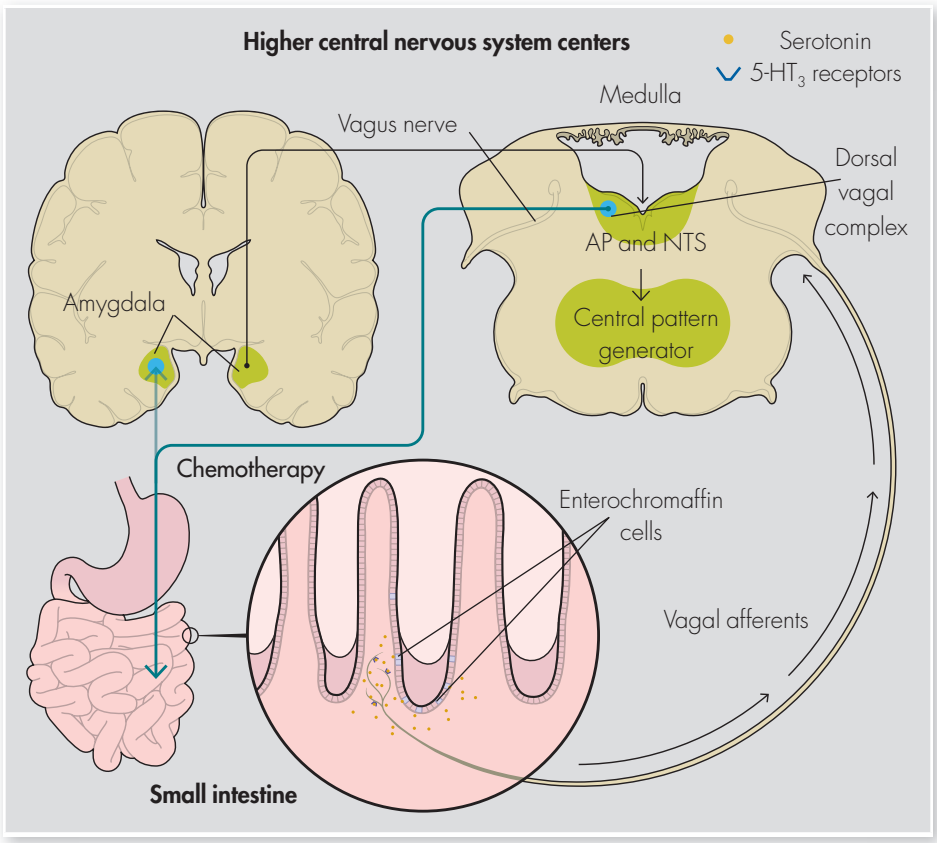
Historical background

The central nervous system plays a critical role in the physiology of nausea and vomiting. It serves as the primary site that receives and processes a variety of emetic stimuli and also has a primary role in generating efferent signals. These signals are

sent to a number of organs and tissues in a process that eventually results in vomiting. Specifically, signals associated with luminal contents are detected by vagal afferent chemoreceptors in the mucosa and relayed to the hindbrain by a rapid and distinctive fire [14].

Mechanisms of chemotherapy-induced nausea and vomiting

Three key components involving areas in the hindbrain and the abdominal vagal afferents have been identified (see figure below). At the time of this guide's publication, it is thought that the existence of an anatomically discrete vomiting center is unlikely [11]. The locations of neurons that coordinate the bodily functions associated with emesis are spread throughout the medulla, supporting the notion that a central pattern generator coordinates the sequence of behaviors during emesis. The central pattern generator receives indirect input from both the area postrema (chemoreceptor trigger zone) and the abdominal vagus by means of the nucleus tractus solitarius.



Pathways by which chemotherapeutic agents produce an emetic response. 5-HT_3, 5-hydroxytryptamine-3 receptor; AP, area postrema; NTS, nucleus tractus solitarius.

How chemotherapeutic agents produce an emetic response

Chemotherapy agents may cause emesis through effects at a number of sites. The mechanism that is best supported by research involves an effect on the upper small intestine. After the administration of chemotherapy, free radicals are generated, leading to localized exocytotic release of serotonin from the enterochromaffin cells; serotonin then interacts with 5-hydroxytryptamine-3 (5-HT_3) receptors on vagal afferent terminals in the wall of the bowel. Vagal afferent fibers project to the dorsal brain stem, primarily to the nucleus tractus solitarius, and, to a lesser extent, the area postrema, the two parts of the brain referred to collectively here as the dorsal vagal complex. Receptors for a number of neurotransmitters with potentially important roles in the emetic response are present in the dorsal vagal complex (as discussed below). These include the neurokinin-1 (NK-1), 5-HT_3, and dopamine D_2 receptors, which bind to substance P, serotonin, and dopamine, respectively. Efferent fibers project from the dorsal vagal complex to the final effecter of the emetic reflex, the central pattern generator, which is an anatomically indistinct area occupying a more ventral location in the brain stem. Receptors for other locally released mediators, such as substance P, cholecystokinin, and prostaglandins, are also present on the vagal afferent terminals. However, the extent to which these mediators are involved at this peripheral site is unknown. Chemotherapy agents may also induce emesis through an interaction with the area postrema within the dorsal vagal complex. Other potential sources of efferent input that result in emesis after chemotherapy include a number of structures in the temporal lobe, such as the amygdala. Evidence for this pathway is less well established than for other proposed sites of chemotherapeutic action.

Chemoreceptor trigger zone

The chemoreceptor trigger zone is located in the area postrema at the bottom end of the fourth ventricle. It lacks an effective blood–brain barrier and is able to detect emetic agents in both the systemic circulation and the cerebrospinal fluid. The area postrema has afferent and efferent connections with underlying structures, the subnucleus gelatinosus and nucleus tractus solitarius, receiving vagal afferent fibers from the gastrointestinal tract.

Abdominal vagal afferents

The abdominal vagal afferents appear to have the greatest relevance for CINV. A variety of receptors, including 5-HT_3, NK-1, and cholecystokinin-1, are located on the terminal ends of the vagal afferents. These receptors lie in close proximity to the enterochromaffin cells located in the gastrointestinal mucosa of the proximal small intestine, which contains a number of local mediators, such as serotonin, substance P, and cholecystokinin.

Following treatment with cytotoxic drugs, serotonin is released from enterochromaffin cells in the small intestinal mucosa adjacent to the vagal afferent neurons on which 5-HT_3 receptors are located. The released serotonin activates vagal afferent neurons via the 5-HT_3 receptors, which leads ultimately to an emetic response mediated via the chemoreceptor trigger zone within the area postrema. Although the vagal

nerve relays information to the area postrema, most of the sensory information from the vagal nerve is relayed to the tractus solitarius, further interacting with the central pattern generator.

At present, this vagal-dependent pathway is considered the primary mechanism by which most chemotherapeutic agents initiate acute emesis.

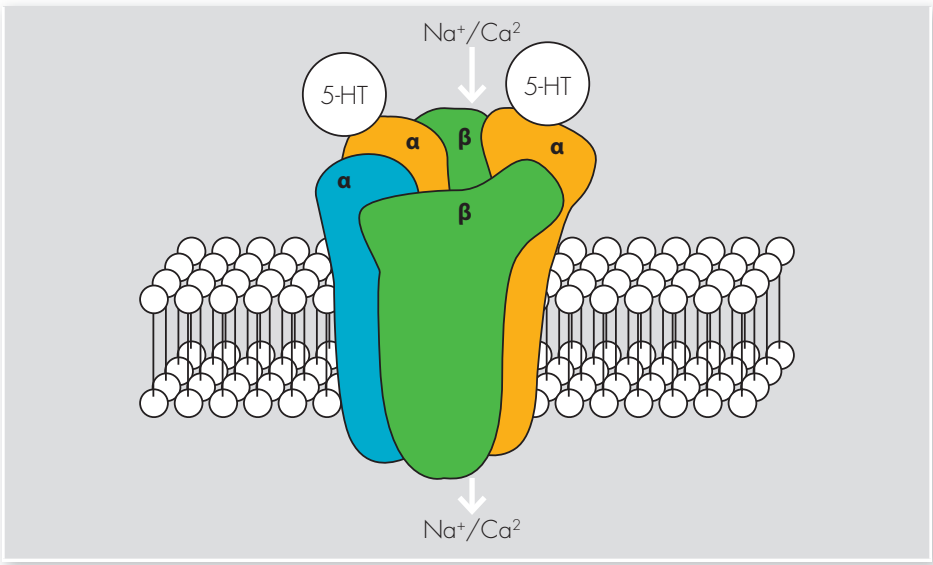
Neurotransmitters

Investigations over the past three decades have gradually elucidated the clinical significance of several neurotransmitters in the vomiting process. The neurotransmitters serotonin, substance P, and dopamine all appear to play important roles in this process [11,15] and will be discussed in more detail below.

Serotonin (5-hydroxytryptamine)

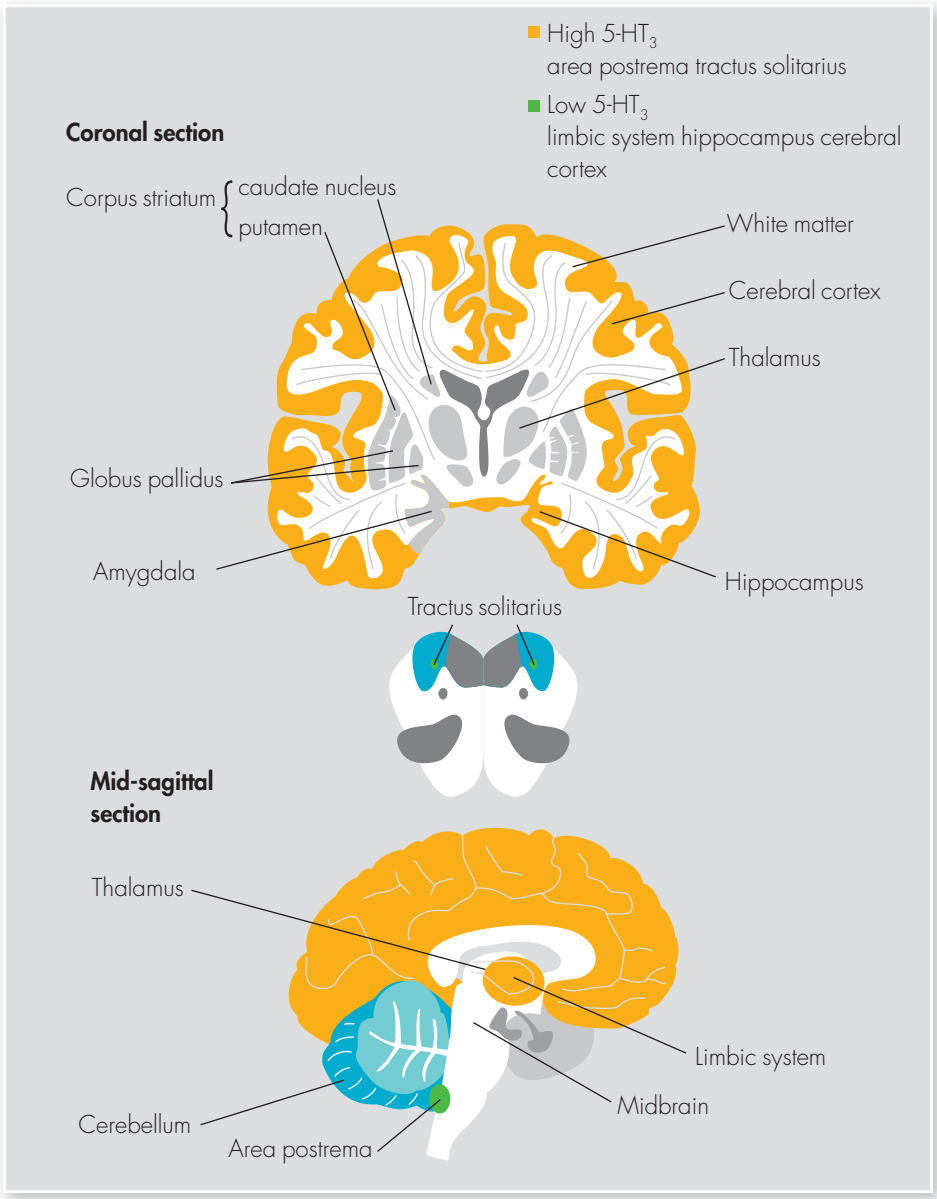
Serotonin is believed to play the most important role in the process of acute CINV, as 90% of the body's stores are located in the enterochromaffin cells. Following exposure to cytotoxic drugs, serotonin is released from enterochromaffin cells in the mucosa of the small intestine, which are next to the vagal afferent neurons where the 5-HT_3 receptors are located.

Of the multiple serotonin receptors identified to date, the 5-HT_3 receptor appears to be most important in the acute phase of CINV, although a role in the delayed phase cannot be completely ruled out. The 5-HT_3 receptor is the only monoamine neurotransmitter receptor that functions as a ligand-operated ion channel (see figure below). It has been identified only in neurons, the central and peripheral autonomic, sensory, and enteric systems.



5-HT_3 receptor. 5-HT, 5-hydroxytryptamine; 5-HT_3, 5-hydroxytryptamine-3.

The highest densities of 5-HT_3 receptors in the brain are located in the area postrema, nucleus tractus solitarius, and dorsal vagal motor nucleus, as depicted in the figure below. They mediate a rapid depolarizing response associated with an increase in membrane conductance following the opening of cation-selective channels; the influx of sodium and calcium contribute importantly to the response. The

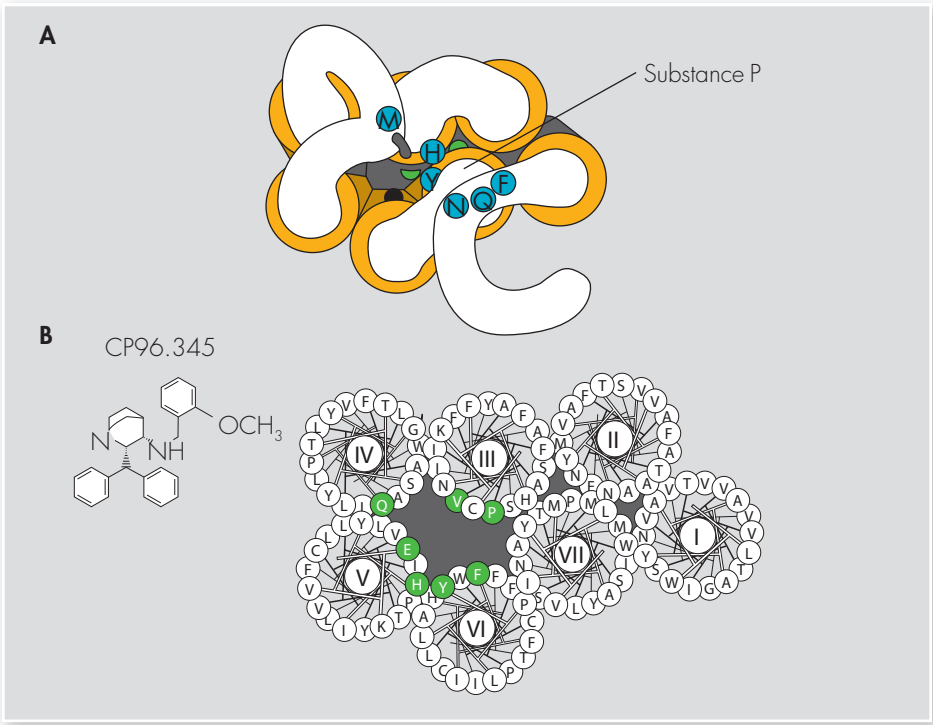


The allocation of 5-HT_3 receptors in the central nervous system. 5-HT_3, 5-hydroxytryptamine-3 receptor. Adapted from Miller et al [16], Moulignier [17], and Peroutka et al [18].

response to serotonin is usually described as a cooperative effect in which the occupation of one receptor subunit enhances the binding of other agonist molecules. The 5-HT_3 receptor has probably evolved to mediate rapid synaptic events. However, it should be noted that in all 5-HT_3 systems examined, repeated challenge to serotonin is met by desensitization and a rapid decline in the amplitude of depolarization.

Substance P and neurokinin-1 receptor

Early research to elucidate the role of this peptide focused on its behavioral and physiological effects in the central and peripheral nervous system. Substance P, the natural ligand of the NK-1 receptor, has been shown to be involved in the transmission of unpleasant stimuli, such as pain, mood disorders, anxiety, stress, and nausea and vomiting. Substance P is a neuropeptide that acts as a neurotransmitter or neuromodulator within both the central and peripheral nervous system by preferentially binding to the NK-1 receptor (see figure below). During the past two decades, multiple studies have suggested that substance P may also be a relevant neurotransmitter in CINV [19]. Animal models demonstrated that the administration of selective NK-1



Neurokinin-1 receptor. **A,** The interaction sides for substance P are shown as blue circles; **B,** The seven transmembrane segments are shown as helical wheels (I to VII), and the interaction points for the prototype nonpeptide antagonist CP-96,345 are shown by green circles. Reproduced with permission from Hokfelt et al [21].

receptor antagonists caused substantial antiemetic efficacy across a broad range of emetic stimuli [20].

Dopamine

Dopamine interacts with dopamine D_1 and D_2 receptors. The dopamine D_2 receptor, located in the chemoreceptor trigger zone, is in part responsible for CINV. In early antiemetic trials in the 1960s, attention was mostly paid to agents that block dopamine receptors. Currently, it is recognized that the antiemetic effect of high-dose metoclopramide is probably due to 5-HT_3 receptor antagonism [22]. Certain side effects associated with dopamine D_2-receptor antagonism include hyperprolactinemia and extrapyramidal symptoms (eg, akinesia, acute dystonic reactions) [23].

Antiemetic treatments

The goal of each antiemetic therapy is to prevent CINV. The development of 5-HT_3 receptor antagonists has been one of the most significant advances for patients with cancer [24]. Corticosteroids show good antiemetic efficacy in the prevention of acute and delayed emesis, especially when combined with other antiemetic agents. However, their role is sometimes underestimated. Another group of antiemetics, NK-1 receptor antagonists, has recently been developed. While significant progress has been made with the development of a number of effective and well-tolerated antiemetic treatments, CINV remains a critical side effect of chemotherapy treatment.

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Emetogenic risk of intravenous chemotherapeutic agents			
High (emesis risk >90% without antiemetics)			
Actinomycin D	Cyclophosphamide (>1500 mg/m^2)	Lomustine	Pentostatin
Carmustine	Dacarbazine	Mechlorethamine	Streptozotocin
Cisplatin			
Moderate (emesis risk 30–90% without antiemetics)			
Alemtuzumab	Carboplatin	Epirubicin	Mitoxantrone (>12 mg/m^2)
Altretamine	Cyclophosphamide (<1500 mg/m^2)	Idarubicin	Oxaliplatin
Azacitidine	Cytarabine (>1 g/m^2)	Ifosfamide	Temozolomide
Bendamustine	Daunorubicin	Irinotecan	Treosulphan
Clofarabine	Doxorubicin	Melphalan IV	Trabectedin
Low (emesis risk 10–30% without antiemetics)			
Asparaginase	Doxorubicin liposomal	Methotrexate (>100 mg/m^2)	Pemetrexed
Bortezomib	Etoposide IV	Mitoxantrone (<12 mg/m^2)	Teniposide
Catumaxomab	5-Fluorouracil	Paclitaxel	Thiotepa
Cetuximab	Gemcitabine	Panitumumab	Topotecan
Cytarabine (<1 g/m^2)	Ixabepilone	Pegasparaginase	Trastuzumab
Docetaxel			
Minimal (emesis risk <10% without antiemetics)			
Bleomycin	Cladribine	Hydroxyurea	Thioguanine
Bevacizumab	Cytarabine (<100 mg/m^2)	α-, β-, γ- Interferon	Vinblastine
Busulphan	Fludarabin	Mercaptopurine	Vincristine
Chlorambucil	Hormones	Methotrexate (<100 mg/m^2)	Vinorelbine

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Emetogenic risk of oral chemotherapeutic agents			
High (emesis risk >90% without antiemetics)			
Hexamethylmelamine	Procarbazine		
Moderate (emesis risk 30–90% without antiemetics)			
Cyclophosphamide	Imatinib	Temozolomide	Vinorelbine
Low (emesis risk 10–30% without antiemetics)			
Capecitabine	Everolimus	Lapatinib	Sunitinib
Etoposide	Fludarabine	Lenalidomide	Thalidomide
Minimal (emesis risk <10% without antiemetics)			
Chlorambucil	Gefitinib	Melphalan	Sorafenib
Erlotinib	Hydroxyurea	Methotrexate	6-Thioguanine

The emetogenic risk of intravenous and oral chemotherapeutic agents. Based on data from:

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