Current Considerations in Managing Chemotherapy-induced Nausea and Vomiting

a report by

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Chemotherapy-induced nausea and vomiting (CINV) has long been a nightmare, primarily for patients with cancer but also for nurses and oncologists. Those who were working in chemotherapy delivery units in the 1970s remember nurses rushing from one patient to the next with basins, trying to hide a vomiting patient from the others. For the patients, CINV caused considerable discomfort and anxiety, and sometimes dehydration and electrolyte imbalance requiring medical intervention including hospitalisation and, occasionally, compliance problems. In a survey conducted by Coates in 1983,[1] CINV was rated as the most distressing side effect of chemotherapy, whether it was vomiting ('being sick'; number one) or nausea ('feeling sick'; number two). The first successful attempt to control CINV was by Gralla[2] with very high doses of metoclopramide, a benzamide substitute favouring gastrointestinal motility. With his regimen CINV could be controlled even in patients receiving high-dose cisplatinum for non-small-cell lung cancer. However, the regimen was cumbersome, requiring dosing every two hours, and not devoid of side effects, especially in young patients.

During the 1980s we gained better understanding of the biological mechanisms of CINV and particularly of the role of 5-hydroxytryptamine (5HT) or serotonin released by enterochromaffin cells of the gut and of the receptors, mainly the type 3 receptor, for this molecule located in the brainstem. This resulted in the development of antagonists of the type 3 receptor of 5HT (5HT3-RA), which received the class name of setrons. Setrons proved to be highly efficacious with an excellent tolerance profile. From that time on, CINV was considered as much more manageable, at least on day one of chemotherapy administration, and setrons became the standard of care.[3] Further improvements came from the development of combinations of antiemetic drugs and, more recently, from the development of a new class of antiemetic drugs, the antagonists of the receptor of neurokinin 1 (NK1-RA).[4]

However, not everything is totally and satisfactorily solved: 20–30% of patients remain refractory to the best antiemetic regimens we have today. Delayed CINV (beyond day one after chemotherapy dosing) has been poorly addressed in early studies and has proved to be a significant residual problem. Similarly, nausea without vomiting, whether early or late, is still present in up to 50–60% of patients, and is all the more poorly perceived because doctors and nurses have spoken of CINV as a solved problem.[3] In another survey published in 1999 by Lindley et al.,[4] nausea was still ranked number one and vomiting number four among the unpleasant side effects of chemotherapy.

Emetogenic Potential of Chemotherapeutic Drugs and their Combinations

The emetogenic risk associated with chemotherapy depends on the drug used, the dose and the combination. There are also patient-associated risk factors. Young patients, those prone to motion sickness or women who experienced emesis during pregnancy have a higher risk associated with chemotherapy. Alcohol users are at lower risk.

Several classifications of chemotherapy drugs according to their emetogenic potential have been published. Discrepancies between these classifications are minimal. Reproduced here (see *Table 1*) is the one proposed by the Multinational Association of Supportive Care in Cancer (MASCC), which distinguishes between drugs with minimal (fewer than 10% of patients at risk), low (10–30%), moderate (30–90%) and high (virtually all patients) emetogenic potential. While these classifications usually consider the dose of the drug as relevant to classify the emetogenic potential (cyclophosphamide, cytarabine), they do not consider their use in combinations, which is quite usual. It is generally accepted that a combination of two or more drugs with emetogenic potential results in the combination being in the emetogenic class one level higher than the most emetogenic compound given alone. A particular example is that of the combination of adriamycine (or dose-equivalent other anthracyclins) and cyclophosphamide, a doublet commonly used in the treatment of breast cancer, whether in advanced disease or in the adjuvant setting. Most authors agree that this combination is on the borderline between moderately and highly emetogenic chemotherapy, patient-related risk factors being of utmost importance.

Antiemetic Drugs

Setrons

Setrons are now the backbone of antiemetic therapy to control CINV. Five setrons are marketed today, not all of them in all countries. They have a number of common properties: they all bind to the 5HT3 receptor with high

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Table 1: Emetic Potential of Chemotherapeutic Drugs (Single Intravenous Agents)

High	Cisplatin	
	Mechlorethamine	
	Streptozocin	
	Cyclophosphamide ≥1,500mg/m^2	
	Dacarbazine	
Moderate	Oxaliplatin	Doxorubicin
	Cytarabine >1gm/m^2	Daunorubicin
	Carboplatin	Epirubicin
	Ifosfamide	Idarubicin
	Cyclophosphamide <1,500mg/m^2	Irinotecan
Low	Paclitaxel	Mitomycin
	Docetaxel	Gemcitabine
	Mitoxantrone	Cytarbine ≤100mg/m^2
	Topotecan	5-fluorouracil
	Etoposide	Bortezomib
	Pemetrexed	Cetuximab
	Methotrexate	Trastuzumab
	Doxorubicin HCL liposome injection	
Minimal	Bleomycin	
	Busulfan	
	2-chlorodeoxyadenosine	
	Fludarabine	
	Vinblastine	
	Vincristine	
	Vinorelbine	
	Bevacizumab	

Source: MASCC, 2005.

affinity (although it may vary from one drug to another, resulting in different recommended doses) and the binding is highly stable; they are active in preventing acute nausea and vomiting (within 24 hours from chemotherapy dosing) and much less so in preventing delayed CINV, with the possible exception of palonosetron; the lowest active dose is the best regimen for each of them, no dose–response relationship having ever been demonstrated above that dose; although early studies found some benefit in giving rescue doses in patients having a suboptimal result in acute CINV, there is no convincing evidence that repeating dosing will improve the results; similarly, if chemotherapy is given on day one only, repeating dosing beyond day one will not efficiently prevent delayed CINV,[7–10] or at least not better than steroids or dopamine receptor antagonists; finally, they all share a common and favourable tolerance profile, the main side effects being manageable constipation, sometimes headache or individual manifestations of intolerance. Surveys and cross-over studies[7] have shown that patient preference can equally favour one drug or another.[3,11,12]

> Young patients, those prone to motion sickness or women who experienced emesis during pregnancy have a higher risk associated with chemotherapy. Alcohol users are at lower risk.

Regarding differences between setrons, beside the recommended doses (see *Table 2*) four of them are available both orally and intravenously (IV). Studies have shown similar efficacy between oral and IV administration, although many physicians and patients still favour the IV route, because of tradition, compliance, a feeling of more security and simplicity since the patient will, most often, undergo venous access for chemotherapy administration. In three randomised studies,[13–15] palonosetron given alone proved to be superior to ondansetron and dolasetron, respectively, also given alone, both in preventing nausea and in preventing delayed CINV. However, neither ondansetron nor dolasetron is given any more without steroids. International guidelines issued by the American Society of Clinical Oncology (ASCO) or MASCC do not recommend one particular setron over the others.

> In the human, the first emetic episode after high-dose cisplatin therapy can occur as late as day seven following dosing.

Steroids

Steroids were used to control CINV even before the era of setrons and proved to be helpful, although much less so than setrons. Today, they can be given alone for low emetogenic chemotherapy but are essentially almost obligatory partners to setrons for moderately to highly emetogenic chemotherapy. Repeating doses on several days, most often three, is the rule since it seems the best way to control delayed CINV.[8] Oral dexamethasone is the most used, with initial dosing of 20mg for highly emetogenic chemotherapy and 4–8mg twice daily over three to four days. Methylprednisolone can also be used, 16mg of methylprednisolone being equivalent to 4mg of dexamethasone. At these doses, steroids are not devoid of side effects, especially in the setting of dose-dense regimens for chemotherapy, given every two weeks or even more frequently. They can induce headache, flushes and insomnia and contribute to weight gain. Most experts agree that being able to diminish the steroids given to control CINV would be significant progress.

NK1-RA

Neurokinin 1 receptors, like 5HT3 receptors, are located in the chemotherapy trigger zone (CTZ) of the brain stem and contribute to the emetic reaction following chemotherapy. Aprepitant is the only NK1-RA commercially available today, but other compounds are under clinical development and should become available in the near future. Aprepitant is an orally available drug and, following the registration study by Hesketh,[16] is recommended over three days, 125mg on day one and 80mg on days two and three, in combination with setrons and steroids in highly emetogenic chemotherapy regimens.[17,18] Whether aprepitant should be given prophylactically from the first cycle of chemotherapy, or only after the suboptimal result of a regimen without this drug, is still under debate.

Other Drugs

Dopamine receptors are present in the CTZ of the brain stem and dopaminergic receptors antagonist drugs contribute to control of CINV.

Two drugs are commonly used in this setting: metoclopramide, the first drug historically active to control CINV, and alizapride. Both are usually prescribed in combination with setrons and steroids with or without aprepitant. They are usually given over several days, with the aim of prevention of delayed CINV, and are often recommended by physicians as 'rescue drugs' freely usable by patients at home. Although they are 'old' drugs, with which oncologists are highly familiar, there have been no formal studies on these drugs since the availability of setrons, and therefore there are no official recommendations on their use. The same applies to domperidone, a drug that is mainly a promoter of gastrointestinal motility, but also a dopaminergic receptor antagonist.

Olanzapine, an atypical antipsychotic drug that antagonises multiple receptors, including 5HT-3, is currently being actively developed in this indication.[19] Neuroleptics such as haloperidol, or even anaesthetic drugs such as propofol, have also been reported and used to control CINV. Owing to their side effects and unfriendly use, they must be restricted to highly refractory cases such as onset of total failure of conventional regimens, a rare situation.

Guidelines

Guidelines have been published and updated by both ASCO and MASCC. They are freely accessible on the websites of these societies and discrepancies between guidelines are only marginal. By and large, no setron is selected as better than the others despite the three phase III trials mentioned above (because the comparator was not given in combination with steroids, the standard practice today). Three drug combinations are recommended for highly emetogenic chemotherapy, mainly with full-dose cisplatinum or high doses of other emetogenic drugs or combinations; two drug combinations (setrons + steroids) are recommended for moderately emetogenic chemotherapy and one drug or even no prophylaxis and only rescue for low or minimal emetogenic potential.

Current Issues

Despite the major progress achieved with setrons and combinations in control of CINV, not all problems are actually solved.

Delayed Chemotherapy-induced Nausea and Vomiting

Most early and registration studies on new antiemetic drugs have focused on acute CINV that occurs within 24 hours of chemotherapy dosing. Both the survey by Lindley[6] and the study by Grünberg[5] proved that delayed CINV is a real problem. Early experimental studies on the ferret showed that setrons were inactive in delayed CINV and were even more active in delaying the first emetic episode rather than reducing the total number of emetic episodes.[20] In the human, the first emetic episode after high-dose cisplatin therapy can occur as late as day seven following dosing. Optimal control of acute CINV from the first cycle of chemotherapy is the best known predictor of absence of delayed CINV, thus emphasising the importance of optimally tailored prophylaxis from the beginning, avoiding the need of 'rescue' drugs or regimens.[8,9] It is known through three prospective randomised studies that delayed CINV is not better prevented by re-dosing setrons on days following chemotherapy than with more classic drugs like metoclopramide. It is usually thought that prolonged steroid therapy combined with metoclopramide is the backbone of management of delayed CINV, although no formal prospective study has proved this approach to be superior to others. In three prospective randomised studies palonosetron has been compared with ondansetron or dolasetron. The studies were initially designed without steroids, although amendments later authorised the adjunction of these drugs. In all three studies, palonosetron proved superior to the comparator on control of delayed CINV as well as nausea over five days. These trials were criticised because of the absence of steroids in some patients, as the combination of setrons and steroids is now standard. However, as the percentage of patients receiving steroids was similar in different arms, it may well be that the superiority of palonosetron is real, even if it has not been acknowledged in the international guidelines.

Table 2: Emetic Potential of Chemotherapeutic Drugs (Single Oral Agents)

High	Hexamethylmelamine	
	Procarbazine	
Moderate	Cyclophosphamide	Vinorelbine
	Etoposide	Imatinib
	Temozolomide	
Low	Capecitabine	
	Tegafururacil	
Minimal	Chlorambucil	6-thioguanine
	Hydroxyurea	Methotrexate
	L-phenylalanine mustard	Gefitinib

Source: MASCC, 2005.

Table 3: Recommended Doses of Serotonin Receptor (5-HT$_3$) Antagonists for Acute Emesis

Agent	Route	Dose
Ondansetron	IV	8mg or 0.15mg/kg
	Oral	16mg*
Granisetron	IV	1mg or 0.01mg/kg
	Oral	2mg (or 1mg**)
Dolasetron	IV	100mg or 1.8mg/kg
	Oral	100mg
Tropisetron	IV	5mg
	Oral	5mg
Palonosetron	IV	0.25mg

** Randomised studies have tested the 8mg twice-daily schedule.*
*** The 1mg dose preferred by some panelists: small randomised study in MEC, phase II study in HEC.*
Source: MASCC, 2005.

Similarly, nausea was rated the number one side effect of chemotherapy in the Lindley survey and was proved to be severely underestimated by medical or nursing staff in the Grunberg study. Full evaluation of nausea over at least five days should be a priority of any future study on antiemetic therapy, since it is fair to say that delayed CINV remains an unsolved problem today.[9]

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Refractory Patients

A significant minority of patients, maybe up to 15%, still do not have adequate prevention of acute CINV, despite most up-to-date regimens

combining setrons, steroids and NK1-RA. Some of them experience highly debilitating repeated vomiting and retching episodes, suggesting a mechanism different from those that can be effectively blocked by available receptor antagonists. In addition to the immediate major discomfort and potentially severe hydroelectrolytic imbalances, these patients are at high risk of delayed CINV and anticipatory nausea and vomiting at the time of next chemotherapy cycle. They represent a real challenge. It is among this subpopulation that there are patients who refuse to continue therapy and who may compromise the control of their neoplasia. Little is known about the physiopathology of vomiting in these patients. At the author's centre, there was recently one such patient who twice had horrible experiences in adjuvant therapy of breast cancer and was about to refuse further therapy. Conventional-dose benzodiazepines, without continuation of other antiemetic drugs, solved her problem for the third cycle and on to the end of her adjuvant programme. Exceptional therapies have been tested for these stressful situations, including neuroleptics and anaesthetic drugs such as propofol. No standard approach can be recommended yet, and additional fundamental knowledge is probably required for elaborating new standards.

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Fortunately, failure is not always as dramatic as described above, and the majority of 'failing' patients have a few emetic episodes or moderate to severe nausea, sufficient to classify them as failures. In these patients the addition of extra drugs to the classical triad can be sufficient to control CINV. These additional drugs can be benzodiazepines, dopamine receptor antagonists or pro-kinetic drugs, or even low-dose neuroleptics. In this situation, the question is one of balance between the discomfort of suboptimally controlled CINV and the side effects of the additional drugs. Some patients will finally prefer to remain nauseous for some hours or a few days rather than experiencing dizziness, hypersomnia and ataxia as side effects of these cocktails of drugs. The 'deal' has then to be discussed between the patient and the physician.

The Role of Accessory Drugs

There is a severe lack of well-designed studies to define the role and potential of these drugs, whether dopaminergic, pro-kinetic, antipsychotic drugs such as olanzapine, benzodiazepines or other anxiolytic drugs. It is difficult to conduct such studies now because the backbone of antiemetic therapy is considered so well established. In addition, new drugs such as alternative NK1-RAs also have to be tested. Re-exploring old drugs has never been a priority of pharmaceutical companies. However, we have to be conscious that we need these drugs and these studies to provide optimal control of CINV to cancer patients, if possible with no side effects. ■

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Patrick Schöffski
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