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 Gralla2 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.5 In another survey published in 1999 by Lindley et al.,6 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 Adriamycin (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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Cancer-related Complications

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

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cisplatin</td>
<td>Daunorubicin</td>
<td>Paclitaxel</td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td>Mechlorethamine</td>
<td>Cytarabine &gt;1gm/m²</td>
<td>Docetaxel</td>
<td>Bucllan</td>
</tr>
<tr>
<td></td>
<td>Streptozocin</td>
<td>Carboplatin</td>
<td>Mitoxantrone</td>
<td>2-chlorodeoxyadenosine</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide ≥1,500mg/m²</td>
<td>Etoposide</td>
<td>Fluoruridine</td>
<td>Fludarabine</td>
</tr>
<tr>
<td></td>
<td>Darabazine</td>
<td>Cyclophosphamide &lt;1,500mg/m²</td>
<td>Topotecan</td>
<td>Vinblastine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vincristine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vinorelbine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bravuzumb</td>
</tr>
</tbody>
</table>

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

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

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, 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.

**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. 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, flushing 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, 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. 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 has 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.29 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 regimen, 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 cisplatin 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 is recommended for highly emetogenic chemotherapy, mainly with full-dose cisplatin 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 Considerations in Managing Chemotherapy-induced Nausea and Vomiting

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

<table>
<thead>
<tr>
<th>Emetic Potential</th>
<th>Hexamethylmelamine</th>
<th>Procarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Cyclophosphamide</td>
<td>Vinorelbine</td>
</tr>
<tr>
<td>Low</td>
<td>Capetitabine</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Minimal</td>
<td>Chlorambucil</td>
<td>6-thioguanine</td>
</tr>
<tr>
<td></td>
<td>Hydroxyurea</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>L-phenylalanine mustard</td>
<td>Gefitinib</td>
</tr>
</tbody>
</table>

Source: MASCC, 2005.

Table 3: Recommended Doses of Serotonin Receptor (5-HT₃) Antagonists for Acute Emesis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>IV</td>
<td>8mg or 0.15mg/kg</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>16mg*</td>
</tr>
<tr>
<td>Granisetron</td>
<td>IV</td>
<td>1mg or 0.01mg/kg</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>2mg (or 1mg**)</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>IV</td>
<td>1mg or 1.8mg/kg</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>100mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100mg</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>IV</td>
<td>5mg</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>5mg</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>IV</td>
<td>0.25mg</td>
</tr>
</tbody>
</table>

* 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.

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.

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.

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.
Cancer-related Complications

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.

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.

3. Perez EA, Review of the preclinical efficacy and comparative knowledge is probably required for elaborating new standards.
First Announcement

20th EORTC - NCI - AACR Symposium on “Molecular Targets and Cancer Therapeutics”

Geneva, Switzerland, 21 - 24 October 2008

Dear Colleagues,

We cordially invite you to Geneva, Switzerland, to participate in the 20th EORTC-NCI-AACR Symposium on “Molecular Targets and Cancer Therapeutics” from 21 to 24 October 2008.

This symposium, hosted by EORTC, NCI and AACR, will bring together academics and scientists and representatives from the pharmaceutical industry to discuss innovation in drug development, target selection and the impact of new discoveries in molecular and cell biology.

Understanding the pathways and mechanisms which cause cancer and regulate the biological behaviour of tumor cells has led to the development of numerous new agents and innovative targets for clinical trials. This conference has been organised to reflect the many recent advances in the early development of promising new compounds, which are on different stages of preclinical and clinical development. It will bring together delegates from all over the world igniting a huge exchange of information and promoting and developing global partnerships in translational research.

The conference has been developed to ensure the maximum amount of interaction and discussion. We hope that the plenary sessions and the workshops will be informative and lively with extensive discussions.

We are all looking forward to seeing you in Geneva!

Patrick Schöffski
Scientific Chairman

Martine Piccart
Conference Chair

Further information will be available on the EORTC website:
Articles include:

- Current Treatment Standards in Metastatic Colorectal Cancer – The Role of Anti-epidermal Growth Factor Antibodies
  Eric Van Cutsem

- High-dose-rate Brachytherapy of Prostate Cancer
  D Jeffrey Demanes and Dennis R Hill

- Treatment of Multiple Myeloma Patients Who Have Received at Least One Prior Therapy
  Jean-Luc Harousseau

- Targeting the ErbB Family in Head and Neck Cancer
  Pol M Specenier and Jan B Vermorken

- Breast Cancer and Novel Therapeutic Treatments
  John R Benson

- Regional Hyperthermia as Targeted Therapy in the Management of High-Risk Soft-tissue Sarcoma
  Rolf D Issels