

# The Development of Future Research Strategies from Reviewing Antiemetic Trials for Chemotherapy Induced Emesis

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**Abstract:** In reviewing the latest trials of antiemetic usage to prevent cytotoxic chemotherapy induced emesis, gaps in the literature suggest directions for future research and identify methodological approaches to be used in future investigations. The usage of molecular techniques and the identification of new receptors may allow new antiemetics to be developed and identification of the genes coding for antiemetic receptors may be used to select the appropriate antiemetics for individuals. Given the success achieved in controlling post chemotherapy vomiting, future studies should focus upon the control of nausea, and measure the impact of antiemetic control on quality of life as well as evaluating the pharmacoeconomics of these agents. Accounting for the interaction of antiemetics with cytotoxics becomes more important in trial design with the increasing complexity of antiemetic regimens. More information is needed on the emetic potential of the various combination chemotherapy regimens, multiple day chemotherapy and chemotherapy over multiple cycles. The emetic potential of prolonged administration of oral chemotherapy and newer biologicals and targeted therapies needs to be recorded. Further studies are required in specialized areas such as with high dose chemotherapy, for radiation induced emesis and in pediatrics.

**Keywords:** Antiemetics, methodology, guidelines, prognostic factors, quality of life, health economics.

## INTRODUCTION

A review of the most recent antiemetic trials allows for the identification of gaps in understanding methodological issues in study design and directions for future research. It is desirable that these insights be documented as a guide for prioritizing further studies.

The initial drugs used to control acute cisplatin-induced emesis were dopamine antagonists, particularly metoclopramide in high doses, but these were associated with sporadic extrapyramidal reactions and limited efficacy [1]. The breakthrough in acute chemotherapy induced emesis came when it was discovered that the 5-HT<sub>3</sub> receptor antagonists, of which ondansetron was the initial example, ameliorated cisplatin-induced acute emesis in over 80% patients, particularly in combination with dexamethasone [2]. Delayed emesis was only controlled in up to 50% of patients. Subsequently, the NK<sub>1</sub> receptor antagonists were shown to control delayed vomiting after chemotherapy in up to 75% of patients when used in combination with 5-HT<sub>3</sub> receptor antagonists and steroids [3].

New antiemetic regimens should not only prove statistically significantly superior to established treatments in randomized trials, but this should translate into clinically meaningful improvements in the control of nausea and vomiting. This, in turn, enhances the patients' quality of life whilst receiving cytotoxics. As antiemetic regimens become more complex, economic factors must also be considered. Recent trials have advocated triple anti-emetic regimens for

chemotherapy of high emetic potential. In order to identify future research questions and methodological issues I will first review the recent phase III trials adding a neurokinin<sub>1</sub> receptor antagonist to 5hydroxytryptamine<sub>3</sub> antagonists and dexamethasone to control emesis from chemotherapy of high emetic potential. These were performed according to the current best standard methodology, yet raise issues to allow review of the methodology of future trials.

## Review of Aprepitant Trials with Chemotherapy of High Emetic Potential

Two pivotal phase III trials of similar design have been reported for adding aprepitant to 5HT<sub>3</sub> receptor antagonists and dexamethasone in the acute phase of emesis and then continuing into the delayed phase for cisplatin chemotherapy. A third trial looked at doxorubicin and cyclophosphamide using a similar approach. One of the cisplatin trials was from South America and the other from North America, Europe and Australia [3,4].

The eligibility criteria for both cisplatin studies were patients receiving their first ever cycles of cisplatin (>70 mg/m<sup>2</sup> over 3 hours). The control arms in both trials were ondansetron 32 mg, 30 minutes prior to cisplatin with dexamethasone 20 mg orally on day 1 and 8 mg orally twice daily on days 2 to 4. In the aprepitant arm, patients received aprepitant 125 mg orally 1 hour before cisplatin with dexamethasone 12 mg orally on day 1, then aprepitant 80 mg orally on days 2 and 3, with dexamethasone 8 mg daily and dexamethasone 8mg alone on day 4.

The total enrollment on both studies was 1099 patients. The overall complete response rate (CR) in the South American trial was 62.7% for the aprepitant group versus 43.3% for the control (p<0.001) and in the international trial

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72.7% for the aprepitant arm and 52.3% for the control arm ( $p < 0.001$ ). For acute emesis the CR rates were 82.8% versus 68.4% ( $p < 0.001$ ) and 89.2% versus 78.1% respectively, favouring the aprepitant groups. However, in the delayed phase of emesis the difference between the groups was greater, 67.7% versus 46.8% ( $p < 0.001$ ) in the South American study and 74.4% versus 55.8% ( $p < 0.001$ ) in the international trial. Previous trials for delayed emesis often failed to reach 50% CR. The differences achieved by aprepitant were sustained over the 5 days post chemotherapy and over 6 cycles of chemotherapy. As has been previously reported in other studies, the control of vomiting was superior to the control of nausea.

The dexamethasone dose was decreased when given with aprepitant because both are metabolized by the p-450 isoenzyme CYP 3A4 which increases the concentration of co-administered dexamethasone two-fold [5]. Interactions are more likely with co-administered oral medications. No interactions with ondansetron or cytotoxics have been detected and 7 different drugs were co-administered with cisplatin without obvious interactions occurring [6]. There is a decrease in the concentration of co-administered ethinyl oestradiol in studies of long term use, so patients are advised to use additional barrier contraceptive methods.

To measure the impact of the control of emesis on quality of life, the Functional Living Index Emesis (FLIE) was used. Logistic regression analysis showed that more patients in the aprepitant groups reported minimal or no impact of chemotherapy induced emesis on daily life, as compared to those on just a 5HT<sub>3</sub> antagonist and dexamethasone (74.7% versus 63.5% South American, 70.4% versus 64.3% international). No differences in response rates were found in different age groups in both the acute and delayed phases of emesis and the impact on the FLIE was similar for older and younger patients.

In the Hesketh *et al.* study, no differences in the control of emesis between males and females were reported in the aprepitant arm (CR was 69.8% males and 77.6% females). In the control group, which mirrors the prior situation reported for the 5HT<sub>3</sub> antagonists, the CR rate was less for females, 38.8% compared to males 60.5%

There were few side effects associated with adding aprepitant to a 5HT<sub>3</sub> and dexamethasone. Most toxicities were similar in the control arm. The most common adverse events with the combination were hiccups, fatigue, headache, constipation, anorexia and mild elevation of liver transaminases.

Aprepitant has also been added to ondansetron and dexamethasone before chemotherapy with cyclophosphamide plus either dexamethasone or epirubicin, in a study of 866 patients [7]. The three drugs were given on day 1 and aprepitant was compared to ondansetron on days 2 and 3. The overall complete response rate over 5 days was better for the aprepitant group 50.8% versus 42.5% ( $p = 0.015$ ). Complete responses were reported in more patients taking aprepitant in both the acute (76% vs 69%,  $p = 0.034$ ) and delayed (55% vs 49%,  $p = 0.064$ ) phases of vomiting. No differences were seen between the groups in the use of rescue medication, which suggests that nausea was not as

well controlled as vomiting. More patients on aprepitant reported minimal or no impact of CINV on daily life, as measured by the FLIE questionnaire (63.5% v 55.6%;  $p = 0.019$ ). The question remains of whether these results could have been improved by adding dexamethasone in the delayed phase of emesis.

### Methodological Issues and Future Research

Three aspects of trial design require review, based on the above studies. The first is the identification of new endpoints, the second is the new issues in designing antiemetic studies and the third is identifying unanswered questions for future studies.

With the high level of control of vomiting achieved by current triple drug therapy (5-HT<sub>3</sub> (5-hydroxytryptamine<sub>3</sub>) antagonist, NK<sub>1</sub> (neurokinin<sub>1</sub>) antagonist and steroid) in the acute control of emesis, it will be important to decide what is a clinically meaningful improvement and what other endpoints could be measured which have a greater scope for improvement. Trial design issues include identifying new prognostic factors to better target antiemetic prophylaxis, and newer drugs may change the significance of older prognostic factors as we saw with the aprepitant trials. As was demonstrated with the aprepitant trials, drug interactions between antiemetics, cytotoxics and the concomitant medications must be considered in trial design, since they may impact upon efficacy and toxicity. Also, for example, the design of studies to investigate agents for delayed emesis must allow for the impact of the agents used to treat the acute phase, and must recognize that with multi-day chemotherapy both acute and delayed emesis overlap.

Future studies will be needed to test antiemetics for high dose chemotherapy, radiation therapy and in children. New rescue regimens will need to be identified when the initial antiemetics fail.

### Endpoints

When there is a control rate approaching 90% for acute cisplatin induced emesis by using triple antiemetic therapy, how can meaningful improvements be detected? Arguments have been advanced which suggest that a clinically meaningful improvement in patient reported outcomes is 10%, with the lowest estimate being 7% [8,9]. This means that if emesis continues as the main endpoint it will be difficult to demonstrate a clinically meaningful improvement with a new agent. Ethically, studies must not compromise the 80-90% response that is the standard. Future studies may not be able to show superiority but should be powered to show non-inferiority if they have other advantages such as more convenient dosing or a more favorable toxicity profile.

### Nausea

A better primary endpoint for future studies may be nausea. Nausea, being a subjective sensation, relies on the patients' reports, and is more difficult to assess. It has the 3 components of severity, duration and frequency, which should be reported, and there seems little difference between using visual analogue scales or discrete scales for measurement [10]. Patient and observer assessments of

outcomes may differ and the frequency of recording endpoints may interact with the endpoint being observed [11].

### Quality of Life

An important endpoint which should be incorporated into phase III trials as it was in the aprepitant studies is the impact of the control of emesis on the patients' overall quality of life. Lindley *et al.* were able to demonstrate the improvement in quality of life as measured by the FLIE (Functional Living Index Emesis) in patients who experienced chemotherapy induced nausea and vomiting as compared to those who did not [12]. This helps to assess the balance between the efficacy and toxicity of the antiemetic regimen.

### Economic Endpoints

Economic endpoints are increasingly relevant to clinical practice and with multidrug antiemetic therapy. Less expensive regimens are preferred if they demonstrate equal results. Economic analyses should be part of randomized trials of new antiemetics and are best designed prospectively by independent health economists. The economic balance will be viewed differently from the perspective of regulators, patients and pharmaceutical companies. Account must be taken of the cost of the drugs, hospital and physician visits but also the opportunity costs, for example the lost of productivity occasioned by severe emesis. A further economic issue is the need to accurately assess the emetic potential of new cytotoxic agents, biologicals and combinations of drugs so that money is not wasted by over-treatment with prophylactic antiemetics.

### Methodological Issues for Future Trial Design

#### The Emetic Stimulus

The emetic potential of the chemotherapy regimen is an important predictor of the likelihood of vomiting and must be considered in designing trials to test new antiemetics. Older cytotoxic agents can be readily assigned to groups according to their emetic potential, but there is much less data available for newer agents. The emetic potential of cytotoxics such as oxaliplatin and pemetrexed requires further definition. The nausea and vomiting associated with targeted therapies and biological agents, such as trastuzumab or imatinib, and oral chemotherapy agents used in prolonged dosing schedules, such as capecitabine, temozolomide and oral idarubicin, have not had their emetic potential well documented. Data on the emetic potential of new agents should be specifically collected in the initial clinical trials of these agents. For oral agents the simple provision of diary cards to patients commenced on these agents would allow collection of these data. Prospective data collection using electronic diaries may increase the accuracy of these data and avoid errors due to backfilling missed observations. In some situations, small studies have been published and the opportunity for an overview and meta-analysis of these data may allow classification of the emetic potential of the new agent.

The most difficult problem in this area, however, is that rarely are cytotoxics given as single agents and the emetic

potential of combinations has not been well documented. Chemotherapy given concomitantly with radiotherapy also provides a challenge to assessing emetic potential, since there are many confounding factors related to the radiotherapy in addition to the chemotherapy drug, dose and schedule.

### Prognostic Factors

Prior to the use of the NK<sub>1</sub> receptor antagonists, the main prognostic factors for controlling emesis were age, gender and alcohol consumption. Younger patients did not respond as well to antiemetics. There was more difficulty controlling post-chemotherapy emesis in females, and a history of a prior alcohol intake of greater than 100g/day was associated with less emesis following cisplatin chemotherapy [13,14,15]. The reason for these observations has not been explained and could be the subject of further research. For example, a postulate that hormones may be responsible for the difference in antiemetic efficacy between the sexes could be studied by comparing pre and post menopausal women, adjusting for age in a large data base generated by multiple antiemetic studies [16]. These prognostic factors, however, changed with the introduction of the NK<sub>1</sub> receptor antagonists. In Hesketh's study which incorporated aprepitant, no differences in response to the antiemetic were dependent on age or gender [4].

New prognostic factors need to be investigated. The emergence of gene array technology identifying the genes coding for the 5-HT<sub>3</sub> and NK<sub>1</sub> receptors may allow clinical correlations and more rational selection of antiemetic regimens for patients. For example, patients with genetic variations in the 5-HT<sub>3B</sub> receptor gene might respond differently to antiemetic treatment [17].

Future trial design may account for functional genetic polymorphisms involving serotonergic, dopaminergic and neurokinin systems. Prospective pharmacogenetic studies investigating, for example, the influence of CYP 2D6 metabolic differences with different serotonin antagonists, may allow more rational drug and dose selection for each individual. The efficacy of antiemetic treatment with ondansetron and tropisetron depends on cytochrome P-450 2D6 (CYP2D6) genotype, therefore the rapid and ultrarapid metabolizers are at risk of being undertreated [18].

Other potential risk factors include the susceptibility to motion sickness or the setting of the chemotherapy [19,20]. Further psychosocial factors need to be explored, as does the issue of whether the expectation of nausea and vomiting is correlated with its occurrence. It would be desirable to create an algorithm to predict the likelihood of patients vomiting, but this may need to wait until further research identifies the prognostic factors relevant to predicting poor responses to triple drug antiemetic regimens.

### Allowing for Drug Interactions

With multi-agent antiemetic regimens, potential drug interactions between the antiemetics, cytotoxics and concomitant medications become more critical, as demonstrated in the aprepitant studies. For example, oral vinorelbine is metabolized by CYP3A4, as are the NK<sub>1</sub>

antagonists, and interactions may become apparent as it is introduced into practice [21]. The interaction between NK<sub>1</sub> antagonists and the efficacy of abdominal radiation has been questioned in the light of animal studies which show amelioration of cisplatin and radiation-induced tissue damage by an NK<sub>1</sub> antagonist [22]. Corticosteroids may also have detrimental interactions. For example, therapeutic concentrations of dexamethasone have been found to attenuate cytotoxicity in human glioma cells exposed to various cytotoxic drugs [23]. Patients receiving the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate-cytarabine) regimen which includes dexamethasone have an increased mortality if they develop hyperglycemia during induction [24]. Long term steroid use with multiple day chemotherapy will compound the problem. It is also important to recognize that large numbers of patients use complementary therapies, which may interact with antiemetics, as is the case with St John's wort which is metabolized by both CYP3A4 and CYP2D6 [25].

### Design of Studies of Delayed Emesis

The ideal design for studies of delayed emesis is to use the same emetic stimulus and same anti-emetics for the acute phase in each arm of a randomized study and then compare the treatments for the delayed phase of the emetic response. This is problematic with the use of NK<sub>1</sub> receptor antagonists, since they have also been found to add to the control of acute emesis, and better control of acute emesis impacts on the incidence of delayed emesis. What further compounds the issue is the long duration of action of the NK<sub>1</sub> antagonists. This has probably been best demonstrated, not by the pharmacokinetic profile alone, but by the duration of receptor blockade which can be demonstrated by PET scanning of the brain after the administration of the drug [26]. The drug given in the acute phase may well have its effect carry over into the delayed phase. It is, therefore, not known what specific efficacy against delayed emesis the NK<sub>1</sub> antagonists would have if only used in the delayed phase. Therefore, the treatment of delayed emesis currently includes an NK<sub>1</sub> receptor antagonist if it has also been used for acute emesis. Currently, the phase III trials support 3 days of an NK<sub>1</sub> antagonist, but is this the optimal dose? The design issue is that antiemetic studies should aim at the minimum effective dose, so that the toxicity of the antiemetic and propensity for drug interactions are minimized. If a longer course of therapy is given initially and is effective it is less likely that further studies will explore shorter courses. This is particularly true with oral therapy which is so easy to administer.

### Methodology of Studies to Assess Multiple Day Chemotherapy

If cisplatin is delivered over multiple days, acute and delayed emesis overlaps. Whereas it may be reasonable to extrapolate from the single dose cytotoxic studies and give triple antiemetic therapy the optimal dosing frequency of the NK<sub>1</sub> antagonist in this situation is unknown. In non-randomized studies it has been observed that the response to single agent ondansetron when used with multiple day cisplatin decreased from 78% on day 1 to 57% on day 5 [27].

The addition of steroids increased antiemetic efficacy over 5 days. It would seem reasonable to add 3 days of an NK<sub>1</sub> antagonist but it is unknown whether less than this will be effective.

With the increasing use of oral cytotoxics and biological agents, which are given continuously over many days, there is no accurate data on how much vomiting occurs because patients are administering these drugs at home, where they are not being observed. There are no data incorporating NK<sub>1</sub> receptor antagonists in this setting. The same issue arises with multiple fractions of radiotherapy.

### The Need to Assess Multiple Cycles of Chemotherapy

The methodological issues of evaluating antiemetic therapy over multiple cycles have been well documented [27]. Over the course of such studies patients drop out. This not only decreases the overall numbers but may also change the balance of prognostic factors over time. Research into antiemetic efficacy over multiple cycles should be done in patients with tumor types which would minimize the dropout rate. Also, statistical techniques need to account for the antiemetic efficacy in a particular cycle being influenced by the response in the previous cycle [28]. Fortunately, in reviewing the data to produce the consensus guidelines, there is additional information incorporating NK<sub>1</sub> antagonists. De Wit *et al.* analyzed the extension phases of the 2 pivotal phase III studies of the addition of aprepitant to ondansetron and dexamethasone. This showed that the antiemetic efficacy as assessed by no emesis and no significant nausea on the aprepitant arms was maintained over multiple cycles (61% for cycle 1 and 59% for cycle 6) [29].

### Future Studies

There are still many possibilities for new anti-emetic agents to be developed as new receptor families such as the opioid, cannabinoid and PYY receptors are further investigated [30,31,32]. New antiemetic regimens such as those incorporating palonosetron as the 5-HT<sub>3</sub> antagonist, and optimal dose and scheduling of the triple drug regimens need further research.

There remain unanswered questions for further trials with the currently available drugs. With cytotoxics of high emetic potential we need to further explore delayed emesis and the optimal dosing of NK<sub>1</sub> receptor antagonists. With chemotherapy of moderate emetic potential the role of both palonosetron, a new 5HT<sub>3</sub> receptor antagonist, and the NK<sub>1</sub> antagonists in both the acute delayed emesis with dexamethasone needs defining. The appropriate control arms of these studies will be identified by the current guidelines.

### Trials for High dose Chemotherapy

The use of chemotherapy in very high doses in myeloablative regimens prior to stem cell or bone marrow transplants, or in the treatment of acute myeloid leukaemia, is a category that has not responded as well to antiemetic regimens which are effective with conventional doses. This may influence other aspects of care, such as the ability to maintain enteral nutrition.

## Trials in Children

There is less evidence to support the interventions used to control chemotherapy induced nausea and vomiting in children, than adults [33]. The introduction of an effective antiemetic into adult medicine should trigger studies specifically in children.

## Trials with Radiotherapy

The use of antiemetics in radiotherapy and the incorporation of new drugs is complex. For each dose the emetic potential is dependent on the dose per fraction and the site and size of the radiotherapy field. Added to this is the complexity of multiple daily fractions. Care should also be taken in prescribing antiemetics for elderly patients where co-morbid conditions and polypharmacy are additional complications [34].

## Studies of Rescue Antiemetics

Since antiemetic drugs are developed for prophylactic use as initial therapy, very little research has been done into antiemetic rescue medication. There will certainly be compassionate use and post marketing surveillance data available on the use of aprepitant for patients who have failed to achieve a complete response to standard therapy in a previous cycle, and then have the NK<sub>1</sub> antagonist added in subsequent cycles. Prospective studies with chemotherapy of high or moderate emetic potential would test the value of adding an NK<sub>1</sub> antagonist, if not used in the first cycle. They would be stratified by prognostic factors and the number of emetic episodes in the preceding cycle, and then a phase II trial could simply test the triple antiemetic therapy of a 5-HT<sub>3</sub> antagonist, dexamethasone plus an NK<sub>1</sub> antagonist in the subsequent cycle. A phase III trial would randomize this triple therapy against the 5-HT<sub>3</sub> antagonist and dexamethasone. The studies would initially study acute emesis and subsequently delayed emesis.

There is little data on the patients who receive triple antiemetic therapy as prophylaxis but need to be rescued within the same cycle. The older drugs such as metoclopramide, prochlorperazine and lorazepam are candidates, but reports are little more than anecdotal and more formal evaluation of a rescue regimen would be useful research. Studies could be designed by selecting patients on the basis of known poor prognostic factors, or patients who had emesis on cycle 1, and identifying a candidate drug such as an NK<sub>1</sub> antagonist if it had not been previously used. The rescue drugs would be given immediately if breakthrough emesis occurred. Alternatively, patients could be pre randomized and given an agent to use for breakthrough emesis.

## CONCLUSION

In reviewing the latest antiemetic studies, we have identified trials that are required in the immediate future because of the emergence of new drugs and the discovery of gaps in the literature. Methodological issues have been identified which require new approaches to areas which are difficult to study. Emerging molecular techniques show great

potential to impact upon on the antiemetic field in predicting the response to antiemetics, and therefore guiding therapy.

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