ANTIEMETIC RESEARCH: SOLVING PATIENT PROBLEMS

Ian N Olver ■ Royal Adelaide Hospital Cancer Centre and University of Adelaide, South Australia
Email: ian.olver@adelaide.edu.au

Abstract

A study which showed that patients ranked nausea and vomiting as their most distressing side-effects of chemotherapy reinforced the need to discover more effective antiemetics. Nausea and vomiting impact on patients' quality of life. It is important to have patients rank their own adverse experiences and this may differ from an observer's assessment. A breakthrough in ameliorating acute post chemotherapy emesis occurred with the introduction of the 5 hydroxytryptamine$_3$ antagonists. However, a repeat of patients' ranking of the severity of side-effects of chemotherapy after the introduction of these drugs still showed nausea and vomiting ranking in the top three. This was due to poor control of delayed emesis, which occurs after 24 hours. A study comparing clinicians' predictions of the severity of patients' emesis against their actual experience post chemotherapy showed that clinicians underestimated delayed emesis by up to 28%. The next development in antiemetics was the advent of the neurokinin$_1$ receptor antagonists. When added to ondansetron and dexamethasone the control of delayed emesis was improved by up to 25%. Patients' experiences of side-effects remains variable. Expectation of nausea for example, can influence the experience of that side-effect. There is a need to repeat a study of patients' perceptions of toxicity to judge the impact of the triple antiemetic therapy regimens.

A study reported by Coates et al in 1983 is often quoted in the antiemetic literature as providing the rationale for the research effort to prevent chemotherapy induced emesis.[1] In this study, 99 patients who had received a range of cytotoxic drugs within the previous week were shown a set of 45 cards with physical side-effects and 28 cards with non-physical side-effects, from which they were asked to select the side-effects they had experienced and subsequently to rank their severity. When all the results were combined for this group of patients, vomiting and nausea were ranked first and second.

Not only are nausea and vomiting distressing side-effects in their own right, but they also adversely impact on the health related quality of life of patients.[2] A group of 832 chemotherapy naive patients who received chemotherapy of high or moderate emetic potential completed both the European Organization for Research and Cancer Core Quality of Life Questionnaire (QLQ-C30) before and after chemotherapy, as well as a self report nausea and vomiting diary. Those patients who reported both nausea and vomiting in comparison with a group who reported neither, had significantly worse physical, cognitive and social functioning, global quality of life, fatigue, anorexia, insomnia and dyspnoea. Those patients who experienced nausea only had less worsening of symptoms. The health related quality of life scores all returned to baseline, or better, within two to four weeks.

Patient versus observer assessments

A strength of these studies is that patients are being asked to assess their own symptoms. In the design of many antiemetic studies both the patient and an observer record the nausea and vomiting. Intuitively one might expect objective criteria may be recorded by observers, particularly if the patients are feeling unwell or their drugs have sedative side-effects. In testing this, Kris and colleagues in a study of nausea and vomiting following high-dose cisplatin, found that the directly observed and patient recalled number of emetic episodes correlated very well ($r = +0.98$, $p < 0.025$).[3] Subjective sensations such as nausea can really only be assessed by the patient and observers would need to question the patient to record their severity. Fetting and colleagues reported a significant relationship between patients self reporting of nausea and that of observers in a study of emesis after high dose cyclophosphamide.

We examined three of our randomised antiemetic studies to investigate the relationship between patient and observer assessments.[4] In one parallel subjects study there was no significant difference between the patients and nurses assessments of the number of vomiting episodes, but the duration of vomiting, the severity and duration of nausea and the side-effects of the antiemetic were given higher scores by the nurses. The high scoring for emesis by the nurses however, may just have reflected their frequent prospective recording as compared to the retrospective recording by the patients at 24 hours. Differences in duration may just reflect differences in the frequency of recording. In two cross-over studies the patients recorded more vomiting episodes than the nurses, while the nurses recorded more anxiety and sedation than the patients. This resulted in the patients detecting a difference in the side-effects of the antiemetics not detected by the nurses. Here the nurses recorded the number of vomiting episodes at the end of an eight hour shift. The result may have been different if they had recorded the number of vomiting episodes each hour as occurred in the parallel design study. Therefore there are differences between patient and observer assessments of nausea and vomiting which may just reflect the method and timing of the collection, but highlight the hazards of comparing data between studies and suggest the limits to the accuracy of relying only on patient reporting.

The 5 hydroxytryptamine$_3$ antagonists

Emesis following chemotherapy became particularly problematic with the introduction of cisplatin in the mid 1970s. It was recognised that antiemetics should be given prophylactically to prevent emesis, but the available drugs were ineffective. The main antiemetics tried were the dopamine antagonists, particularly metoclopramide which blocked the D_2 receptor, thought to mediate emesis.[5] Subsequently, based on animal studies, high doses of metoclopramide, up to 3mg/kg, were more effective for preventing cisplatin induced emesis, but caused more side-effects including sporadic extrapyramidal reactions.[6] It is little wonder that patients rated nausea and vomiting so high in the list of the worst side-effects of chemotherapy.

A breakthrough in the control of acute chemotherapy induced emesis occurred with the recognition that the 5 hydroxytryptamine$_3$ ($5HT_3$) receptors in the small intestine were involved in triggering the acute emetic response to cytotoxics. The first of the $5HT_3$ receptor antagonists, ondansetron, dramatically reduced the acute phase of emesis in the first 24 hours after the administration of chemotherapy. Ondansetron was shown to be superior to high dose metoclopramide regimens for preventing chemotherapy-induced emesis with the mild reversible side-effects of headache, constipation and mild elevations in liver transaminases being the most common side-effects.[7] A $5HT_3$ receptor antagonist combined with dexamethasone became the gold standard given prophylactically to prevent acute post chemotherapy induced emesis.[8] This resulted in complete protection from cisplatin-induced acute emesis ranging from 70-90%.[9]

Patients' perceptions

Ten years after the initial study reported by Coates et al, and following the introduction of the $5HT_3$ receptor antagonists, the study on patient perceptions of the side-effects of chemotherapy was repeated.[10] There was a change in the ranking of side-effects by severity, but nausea was still ranked first. Vomiting was now ranked fifth behind tiredness and hair loss and there was a shift from concerns about physical to psychosocial issues. In exploring the predictors of whether nausea and vomiting were selected as one of the top five symptoms, nausea within 24 hours was the strongest predictor of the nausea ranking, followed by delayed nausea, that is nausea after 24 hours. Delayed vomiting was the most powerful predictor of the ranking of vomiting.

These results were confirmed by others. A French study in 100 patients noted the shift from physical to psychosocial concerns and ranked fatigue as the most severe physical symptom.[11] A trial in the Netherlands replicated Coates' survey in patients who had received $5HT_3$ antagonists and found that nausea and vomiting were still ranked in the top three toxicities.[12]

These results are not surprising when the $5HT_3$ literature is analysed. Although very effective for preventing acute vomiting after chemotherapy, if a $5HT_3$ antagonist and dexamethasone were continued the control of the delayed phase of emesis, which commences after 24 hours and can last for a week, rarely exceeded 50%.[13,14] Moreover nausea was not being controlled as well as vomiting. In a prospective study, despite prophylaxis with ondansetron, the majority of patients experienced nausea, with delayed nausea twice as frequent as acute nausea.[15]

Clinicians' predictions of emesis

With the advent of the $5HT_3$ receptor antagonists, how much nausea and vomiting did clinicians perceive that their patients would experience? Grunberg et al determined the incidence of acute and delayed chemotherapy-induced nausea and vomiting among patients receiving chemotherapy of high (HEC) or moderate (MEC) emetic potential.[16] They also assessed whether doctors and nurses could accurately predict the incidence of acute and delayed nausea and vomiting in their own patients. Twenty-four physicians and nurses from 14 oncology practices in six countries recruited 298 patients. Physicians and nurses accurately predicted the incidence of acute nausea and vomiting, but underestimated the incidence of delayed nausea and vomiting after HEC by 21% to 28% and delayed nausea after MEC by 28%. Moreover delayed symptoms could appear without acute symptoms after HEC (emesis, 38%; nausea, 33%) and MEC (emesis, 19%; nausea, 21%).

Neurokinin$_1$ receptor antagonists

Somewhat fortuitously, the next major breakthrough in antiemetic development addressed the issue of delayed nausea and vomiting after chemotherapy. This was the development of the neurokinin$_1$ receptor antagonists; the first to market being aprepitant.

In two large phase III placebo controlled trials performed in South America (Poli-Bigelli et al) and in centers from North America, Europe and Australia (Hesketh et al), patients receiving their first cycles of cisplatin >70mg/m^2 had aprepitant for three days added to intravenous ondansetron; 32mg 30 minutes before cisplatin with oral dexamethasone 20mg on day one followed by oral dexamethasone, 8mg twice daily from days two to four in the study arm and compared to ondansetron and dexamethasone alone.[17,18] Combining the trials 1099 patients were enrolled. For acute emesis the response in the aprepitant patients was 82.8% versus the control group 68.4% ($p<0.001$) for Poli-Bigelli study and aprepitant 89.2% versus controls 78.1% ($p<0.001$) for Hesketh. The biggest differences were seen in delayed emesis; 67.7% versus 46.8% ($p<0.001$) and 74.4% versus 55.8% ($p<0.001$) respectively. The efficacy of aprepitant was maintained over six courses.[19] Also, more patients receiving aprepitant reported no impact of chemotherapy induced nausea and vomiting on their daily lives.

Similar benefits were seen when aprepitant was used as part of the antiemetic regimen to control the acute and delayed nausea and vomiting after combination chemotherapy with an anthracycline and cyclophosphmide.[20]

Patients' expectations

What is required now is a repeat of the Coates' study to see if the control of acute and delayed emesis by the triple therapy of ondansetron, dexamethasone and aprepitant really has decreased the patients' ranking of post chemotherapy nausea and vomiting as among the most severe of side-effects. We also need to understand more about what influences patients' perceptions of side-effects.

A lack of adequate pharmacological explanations for side-effect variation following chemotherapy suggests psychological factors may contribute to the experience of side-effects. Our research aimed to determine if patients' expectations were associated with toxicities.[21] Eighty-seven chemotherapy-naive patients rated their expectations of 20 common side-effects before treatment and then rated their experiences following their first chemotherapy dose. Subjective side-effects, including inability to concentrate, sleep problems, mood changes, tiredness and nausea, were all influenced by expectation.

Assessing the experience of chemotherapy from the patients' perspectives will focus research activity on the side-effects most problematic to patients. It also allows assessment of whether therapeutic interventions have altered the patients' perceptions. In the antiemetic literature such studies were used to justify the research effort to find new antiemetics, then highlight the limitations of the impact of the $5HT_3$ antagonists. Ultimately the NK_1 receptor antagonists were developed, which proved useful for ameliorating delayed nausea and vomiting after chemotherapy. Now the assessment of the impact on the patients' perceptions of nausea and vomiting needs to be reassessed. Further information is required about the factors which explain differences in the patients' perceptions of the toxicities of chemotherapy. □

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