Cost-Effective Use of Antiemetics

By Steven M. Grunberg, MD [2]

Direct comparison of intravenous and oral 5-HT3 antagonists has shown equivalent efficacy if appropriate doses are given, thus allowing widespread use of the more convenient and economical oral route. Effective antiemesis generates additional cost savings by decreasing the resources necessary for salvage antiemetic preparation and administration, additional physician and nursing evaluation, clean-up and maintenance of the patient area, and possible additional hospitalization necessitated by uncontrolled emesis.

Over the last 40 years, there have been marked advances in the development of chemotherapeutic agents effective against numerous tumor types. This increase in efficacy, however, has been accompanied by an increase in toxicity. Of all the toxicities of chemotherapy, the toxicity most feared by patients has been nausea and vomiting.[1] Thus, prevention and control of emesis has been an important goal both to maintain patient quality of life and to allow delivery of full courses of curative and palliative chemotherapy.

Numerous families of antiemetic agents are now available. Under appropriate circumstances, one may obtain excellent antiemetic control with phenothiazines, butyrophenones, substituted benzamides, cannabinoids, corticosteroids, or serotonin (5-HT3) antagonists. However, these agents differ in terms of efficacy, toxicity, and cost. Effective antiemetic control should never be sacrificed as a cost-cutting measure. However, cost-effective use of modern antiemetics requires selection of the correct drug to be administered by the correct route at the correct dose in the correct clinical setting.

The first antiemetic agent to provide effective antiemetic control against the highly emetogenic chemotherapeutic agent cisplatin (Platinol) was high-dose metoclopramide,[2] which was introduced in the early 1980s. In contrast to the previous clinical reality where virtually all patients had severe vomiting within the first 24 hours after receiving cisplatin, high-dose metoclopramide completely protected against acute vomiting in up to 40% of patients, with even greater protection when corticosteroids were added.[3] Introduction of the 5-HT3 antagonists in the early 1990s represented an additional advantage since these agents provided at least equivalent efficacy while eliminating the potentially severe antidopaminergic toxicity that had limited the use of high-dose metoclopramide. Furthermore, the 5-HT3 antagonists had the added advantage in some comparisons of actually increasing the rate of antiemetic protection. In a direct comparison of a 5-HT3 antagonist and metoclopramide, Marty et al[4] demonstrated complete or major protection from cisplatin-induced acute vomiting in 75% of patients treated with ondansetron (Zofran), compared with 42% of those treated with high-dose metoclopramide. Complete and major control of nausea was also improved by ondansetron; 58% of patients had no more than mild nausea, compared with 42% receiving high-dose metoclopramide. Even greater protection against cisplatin-induced vomiting was achieved through the addition of a corticosteroid. Roila et al[5] demonstrated an increase in complete antiemetic protection from 64% using ondansetron alone to 91% using ondansetron plus dexamethasone.

**5-HT3 Antagonists: Route of Administration and Dosing**

Although the 5-HT3 antagonists are highly effective, the price of these agents has led to questions concerning the most cost-effective method of use. One area of interest has been the identification of the appropriate route of administration. The oral route is particularly inviting since this route has been used effectively with other antiemetics, allows for maximal use of outpatient therapy, and eliminates the necessity for complex preparation of intravenous solutions and for additional personnel and supply costs to administer an intravenous medication. Furthermore, recent studies have shown that antiemetic efficacy is maintained with the oral as compared with the intravenous route of administration. Results from trials by Gralla et al[6] in patients receiving highly emetogenic cisplatin-based chemotherapy and by Perez et al[7] in patients receiving moderately emetogenic...
chemotherapy both demonstrated equivalent efficacy between ondansetron, 32 mg given intravenously, and granisetron, 2 mg orally. These studies, rather than indicating that either agent is intrinsically superior, offer proof of principle that a 5-HT\textsubscript{3} antagonist administered at full dose by the oral route will provide results equivalent to those of a 5-HT\textsubscript{3} antagonist delivered by the intravenous route. Thus, consideration of ancillary costs of administration by these different routes is a legitimate concern.

The 5-HT\textsubscript{3} antagonists have been characterized by an excellent therapeutic index and a wide range of effective doses. If a decrease in dose can maintain full efficacy while realizing a cost saving, then such a change in prescribing patterns would be desirable. DiPiro et al.[8] for example, have shown that in patients receiving cyclophosphamide and doxorubicin, the dose of intravenous ondansetron given with dexamethasone can be reduced from 32 to 20 mg with no significant change in complete protection from vomiting. The basis for this flexibility can be found in the dose-response curve for all of the 5-HT\textsubscript{3} antagonists, which follows an approximately logarithmic rather than a linear pattern; that is, a steep dose-response curve at very low doses until a threshold value is reached and then a relative plateau where little change in rate of complete protection is seen even as dose is significantly increased.[9] When considering the dose-response curve against cisplatin (Figure 1), the dose of ondansetron approved in the United States (32 mg) appears to be well along the plateau rather than at the threshold. Thus, significant dose de-escalation with maintenance of efficacy is possible, and the discrepancy between fully effective doses of ondansetron as defined in the United States and in Europe can be seen as representing different points along the plateau portion of the dose-response curve. On the other hand, the dose of granisetron (Kytril) approved in the United States is just above the threshold of its dose-response curve, and dose de-escalation may thus result in decreased efficacy.

It should be noted that the doses on the curve described above are defined in terms of protection from emesis caused by the highly emetogenic agent cisplatin. The curves could shift to the left (lower threshold value) when considering moderately or mildly emetogenic chemotherapeutic agents, thus making dose de-escalation of all of the 5-HT\textsubscript{3} antagonists possible in this setting. Whether the potential dose de-escalation is of a magnitude sufficient to make these agents economically competitive with the older standard antiemetics (which may also be effective against moderately emetogenic chemotherapy) remains to be seen. Moreover, the dose-response curves may shift to the right in the setting of high-dose chemotherapy, and the appropriate fully effective doses of the various 5-HT\textsubscript{3} antagonists in the bone marrow transplant setting may indeed be higher than doses in common use.

**Anticipatory and Delayed Vomiting**

The data that established the 5-HT\textsubscript{3} antagonists as first-line antiemetics were generated in the setting of protection from acute cisplatin-induced vomiting (vomiting within the first 24 hours after chemotherapy administration). Other forms of chemotherapy-induced emesis may have different mechanisms of action and require different remedies. Anticipatory vomiting is a learned response related to prior failure of antiemetic protection and is best addressed through behavioral strategies. Delayed vomiting is seen 2 to 5 days after the administration of cisplatin[10] and may be multifactorial in origin, with release of serotonin, disruption of gut motility, and cellular breakdown in the gut wall all being potential contributing factors. Corticosteroids appear to be the most effective single agents for the prevention of delayed vomiting, and a combination of a corticosteroid and metoclo- pamide has the best documented efficacy.[11] The Italian Group for Antiemetic Research[12] has demonstrated that a combination of dexamethasone and ondansetron for delayed vomiting is no more effective than a combination of dexamethasone and metoclopramide but considerably more expensive. Some data[13,14] suggest that 5-HT\textsubscript{3} antagonists and dopamine (D\textsubscript{2}) antagonists may have additive or synergistic effects against acute vomiting. These observations could lead to interesting and valuable clinical trials evaluating the efficacy of combined therapy with a corticosteroid, a D\textsubscript{2} antagonist, and a 5-HT\textsubscript{3} antagonist against delayed vomiting. At present, however, the most cost-effective treatment for delayed vomiting is a combination of a corticosteroid and metoclopramide.

**Cost Considerations for Effective Antiemetic Control**

A great deal of emphasis has been placed on the high acquisition costs of the 5-HT\textsubscript{3} antagonist antiemetics as compared to older antiemetics. However, failure of antiemetic protection generates several additional direct costs, including preparation and administration of salvage antiemetics,
increased physician and nurse time spent in evaluation of the vomiting patient, additional costs for clean-up and maintenance of the patient area after vomiting episodes, and additional costs if the patient should require rehospitalization for antiemetic control or correction of fluid and electrolyte imbalance. Thus, maximal prevention of emesis can be highly cost-effective.

Several studies comparing costs of ondansetron and metoclopramide have assessed these factors. Cunningham et al[15] found a 3.7-fold increase in acquisition cost for ondansetron compared with metoclopramide. However, treatment was successful (major protection from vomiting and no adverse events) in 50% of patients receiving ondansetron versus only 22% receiving metoclopramide. When additional costs of management of emesis were taken into account, the cost ratio decreased to 2.3. Ballatori et al[16] compared costs for prevention of cisplatin-induced vomiting in patients receiving ondansetron or metoclopramide, both in combination with a corticosteroid. The drug acquisition cost ratio was 5.2, but this value decreased to 3.2 when the additional emesis management costs were measured. Cox and Hirsch[17] compared costs of antiemetic management in patients receiving cyclophosphamide-based regimens. Patients received either ondansetron and dexamethasone, followed by 5 days of oral ondansetron or metoclopramide and dexamethasone, followed by 5 days of oral metoclopramide. Due to the extended course of administration, the drug acquisition cost ratio increased markedly to 15.0. However, inclusion of costs of antiemetic management decreased this ratio to 2.9.

**Types of Pharmacoeconomic Analyses**

An important factor in pharmacoeconomic analysis of supportive care is the type of analysis used. Three types that may be considered are cost-minimization analysis, cost-effectiveness analysis, and cost-utility analysis.

Cost-minimization analysis is appropriate only when the efficacy and toxicity of two different forms of therapy are identical. Such an analysis might be used, for example, if two 5-HT₃ antagonists were being directly compared, but not if antiemetics with different efficacy rates and different costs for additional management of emesis were being compared.

With cost-effectiveness analysis, these additional factors are included in the assessment. However, this type of analysis often deals with the incremental increase in cost as compared with the incremental increase in survival. Since supportive care measures, such as antiemetic control, increase the tolerability and feasibility of therapy rather than increasing survival, the denominator for classic cost-effectiveness analysis (incremental increase in survival) becomes zero and the calculation cannot be performed.

Another form of pharmacoeconomic analysis appropriate for supportive care is cost-utility analysis. Addition of a utility score to determine quality-adjusted life-years (QALY) eliminates the requirement for a change in survival as long as there is a change in utility, and also effectively quantifies the amount of quality of life that is gained. The present difficulty in performing cost-utility analysis of oncologic supportive care is the lack of well-defined utility scores for these various states of health.

**Pilot Study to Define Utility Scores**

We have begun a series of studies to determine objectively the utility scores for various states of emesis using decision analysis techniques. In a pilot study, 30 patients completing a cycle of chemotherapy were asked to fill out a brief questionnaire.[18] They were asked to assume that any other toxicities experienced (mucositis, alopecia, etc.) had remained the same, and to rate their overall quality of life on a rating scale (visual analogue scale) based on the assumption that there either had or had not been a minimal amount of nausea and vomiting. A marked difference was noted, with 27 of 30 patients stating that quality of life would have been better without vomiting (Figure 2). Moreover, the magnitude of this difference was striking; the mean increase in rating scale score when nausea and vomiting were removed was 52 mm out of a total scale of 100 mm. In an upcoming project, we hope to make finer distinctions between various scenarios of chemotherapy-induced nausea and vomiting using the standard gamble technique. Such decision analysis techniques can then be extended to other areas of oncologic supportive care to provide a more global and quantifiable description of the patient undergoing cancer chemotherapy, and to allow the creation of an aggregate utility score for use in future cost-utility analysis.

**Conclusions**

The development of highly effective but costly agents for the prevention of chemotherapy-induced
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Emesis has focused attention on supportive care as a significant component of the overall economic costs of cancer care. Such attention, however, will be of value if we are encouraged to use available agents in the most logical and fully effective manner while avoiding excessive dosing, unnecessary toxicities, and additional costs. Attempts to apply the principles of formal pharmacoeconomic analysis to antiemetic therapy will advance our understanding of the pitfalls and advantages of adapting such analysis to the general field of oncologic supportive care, and will provide insights into the further integration of supportive care with cytotoxic care as components of the overall cost of treating patients with cancer.

Discussion

Dr. Weeks: You showed a 50-point difference in rating of quality of life by patients depending on whether nausea and vomiting were present. Have you calculated what that kind of quality-of-life benefit might translate into, in terms of cost-effectiveness ratio for drugs effectively controlling nausea and vomiting?

Dr. Gunberg: We have reexamined the data published by Zbrozek et al[1] comparing ondansetron and metoclopramide to see whether we could determine how much of a difference it would make. At least in this data set, when we substituted our experimentally derived utility score parameters, cost-utility analysis showed that replacing metoclopramide with a 5-HT3 antagonist led to an increase of only approximately $4,000 to $5,000 per quality adjusted life year. These results suggested that use of the newer agents was indeed worthwhile.

Reference

References:


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