Cost-Effectiveness of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with Highly Emetogenic Chemotherapy

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ABSTRACT

Objective: Chemotherapy-induced nausea and vomiting (CINV) is a significant problem for cancer patients. Aprepitant, a novel NK-1 receptor antagonist, is approved for use with 5-HT3 antagonists and corticosteroids to prevent CINV associated with highly emetogenic chemotherapy. Nevertheless, the cost-effectiveness of standard aprepitant use has not been established.

Methods: We developed a Markov model to compare three strategies for CINV: conventional treatment with a 5-HT3 antagonist and a corticosteroid, conventional treatment plus aprepitant, and conventional treatment with aprepitant added after the onset of CINV. Data from published clinical trials provided probabilities and utilities for the model. Data from the Centers for Medicare and Medicaid Services and the Federal Supply Scale provided costs for medical resources and medications utilized. Resource use data were based on a randomized clinical trial and routine clinical practice. The incremental cost-effectiveness ratio (ICER) for each aprepitant strategy was calculated in US$ per healthy day equivalent (HDE) and converted to dollars per quality-adjusted life-year (QALY). Univariate and probabilistic sensitivity analyses addressed uncertainty in model parameters.

Results: Adding aprepitant after CINV occurred cost $264 per HDE ($96,333/QALY). The three-drug strategy cost $267/HDE with a 95% confidence range of $248–$305/HDE ($97,429/QALY; $90,396–$111,239/QALY). In univariate analyses, the most influential factors on the ICER were: the cost of aprepitant, the likelihood of delayed CINV without aprepitant, the likelihood of acute CINV with/without aprepitant, and the increase in HDE from avoiding CINV.

Conclusions: Aprepitant provides modest incremental benefits compared with conventional management of CINV. Routine aprepitant use appears most cost-effective when the likelihood of delayed CINV or the cost of rescue medications is high.

Keywords: cost-effectiveness, health-care utilization, nausea and vomiting.

Introduction

Patients frequently cite nausea and vomiting as one of the most distressing and debilitating side effects of chemotherapy [1–6]. Chemotherapy-induced nausea and vomiting (CINV) can be divided into acute (24 or fewer hours after chemotherapy), delayed (more than 24 hours after chemotherapy) or anticipatory (before chemotherapy) [7]. This distinction is made because acute CINV is believed to be mediated through serotonin receptor stimulation while delayed CINV is thought to involve multiple neurotransmitters, including opioid and neurokinin receptors [8]. Chemotherapeutic agents have variable emetogenic potential that is affected by dose and method of administration [9–11]. For example, cisplatin, one of the most emetogenic agents, has rates of acute vomiting approaching 100% in the absence of anti-emetic therapy [12]. Adequate control of CINV is essential to effectively delivery cisplatin and other highly emetogenic chemotherapy.

Ondansetron was the first 5-hydroxytryptamine3 (5-HT3) antagonist approved for use against CINV. Several randomized clinical trials demonstrated the superiority of ondansetron for control of acute CINV when compared with metoclopramide and/or dexamethasone containing regimens [13–18]. Other 5-HT3 antagonists, such as granisetron, dolasetron, and tropisetron, are as efficacious as ondansetron [19]. The combination of a 5-HT3 antagonist plus corticosteroid has emerged as conventional management for prevention of CINV associated with highly emetogenic chemotherapy [20]. Even with conventional management, approximately 20% to 30% of patients receiving cisplatin experience acute CINV [21,22]. Moreover, this regimen appears to provide limited benefits for delayed CINV, with 40% to 50% of patients continuing to experience delayed CINV [23–26].

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Neurokinin-1 (NK-1) antagonists recently have been introduced as a new class of drugs available to prevent and treat CINV. These agents block the interaction of substance P, a neurotransmitter thought to play an important role in the development of nausea and vomiting, with the NK-1 receptor [27]. Aprepitant, the first commercially available NK-1 antagonist, improves control of both acute CINV, when added to a 5-HT3 antagonist and corticosteroid, and delayed CINV, when combined with a corticosteroid [28–30]. The improved efficacy of aprepitant persists over multiple cycles of cisplatin-based chemotherapy [31]. The addition of aprepitant to the armamentarium of antiemetic agents has led to recent changes in treatment guidelines for prevention of CINV. Revised 2005 National Comprehensive Cancer Network guidelines for prevention of CINV now recommend the routine addition of aprepitant to the standard combination of a 5-HT3 antagonist with a corticosteroid when administering highly emetogenic chemotherapy [32].

The primary objective of this study is to determine whether the additional costs associated with adding a NK-1 inhibitor for the prevention of CINV are justified by the additional efficacy and improvement in quality of life. The costs and benefits of a 5HT-3 antagonist and corticosteroid, for the prevention of CINV associated with highly emetogenic chemotherapy, were compared with the following strategies: 1) a three-drug regimen consisting of aprepitant, a 5HT-3 antagonist, and a corticosteroid; or 2) a strategy adding aprepitant to the conventional regimen only after CINV occurs with a prior cycle of chemotherapy.

Methods

Decision Model

We developed a Markov model with a 28-day cycle length to compare costs and clinical outcomes associated with each regimen in a hypothetical cohort of patients receiving a chemotherapeutic regimen including 70 mg/m² or less of cisplatin. The structure of the model is shown in Figure 1. A patient in the model could experience one of four outcomes: 1) neither acute nor delayed CINV; 2) acute CINV only; 3) delayed CINV only; or 4) both acute and delayed CINV. We utilized published data from a randomized clinical trial by Hesketh et al. to establish probabilities for each outcome (Table 1) [28]. Costs were calculated from the payer perspective with results reported in 2005 US dollars. We modeled patient care costs and outcomes over the time horizon from administration.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Probabilities used in the model</th>
</tr>
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<tbody>
<tr>
<td>Probability</td>
<td>Base case</td>
</tr>
<tr>
<td>Standard regimen</td>
<td></td>
</tr>
<tr>
<td>Acute CINV</td>
<td>0.219</td>
</tr>
<tr>
<td>Delayed CINV-acute CINV</td>
<td>0.815</td>
</tr>
<tr>
<td>No acute CINV</td>
<td>0.781</td>
</tr>
<tr>
<td>Delayed CINV-no acute CINV</td>
<td>0.306</td>
</tr>
<tr>
<td>Three-drug regimen</td>
<td></td>
</tr>
<tr>
<td>Acute CINV</td>
<td>0.108</td>
</tr>
<tr>
<td>Delayed CINV-acute CINV</td>
<td>0.692</td>
</tr>
<tr>
<td>No acute CINV</td>
<td>0.892</td>
</tr>
<tr>
<td>Delayed CINV-no acute CINV</td>
<td>0.137</td>
</tr>
</tbody>
</table>

CINV, chemotherapy-induced nausea and vomiting.
Cost-Effectiveness of Aprepitant

of the first cycle of the cisplatin containing chemotherapeutic regimen through a total of five cycles.

Treatment regimens were based on the approved usage of aprepitant as defined in the registration clinical trials. The conventional treatment arm consisted of ondansetron 32 mg IV and dexamethasone 20 mg PO given on day 1 followed by dexamethasone 8 mg PO twice daily on days 2 to 4. The three-drug regimen consisted of ondansetron 32 mg IV, dexamethasone 12 mg PO and aprepitant 125 mg PO on day 1 followed by aprepitant 80 mg PO and dexamethasone 8 mg PO once daily on days 2 to 3 then dexamethasone 8 mg PO on day 4 [28]. The third arm of the model utilized conventional management until the occurrence of acute or delayed CINV and switched to the three-drug treatment regimen for all remaining cycles. The probabilities used in the model and ranges explored in univariate sensitivity analyses were obtained from randomized clinical trial data and are shown in Table 1 [28]. Probability ranges were obtained by constructing 95% confidence intervals for proportions derived from the literature using normal approximations to the binomial distribution [33].

Costs

Costs of care are shown in Table 2. The costs of clinic and laboratory based resources were derived from year 2005 reimbursement data and physicians' fee schedules available from the Centers for Medicare and Medicaid Services (CMS) [34]. Medication costs were obtained from the Federal Supply Scale (FSS) [35,36]. The cost of rescue treatment for CINV included a clinic visit, comprehensive metabolic panel, and prescription for 30 tablets of both metoclopramide 10 mg and ativan 1 mg. It was assumed that drug delivery costs were equal across treatment groups. The antiemetic medications under consideration are well tolerated and typically do not result in adverse events requiring additional medical attention. In the probabilistic sensitivity analysis, all cost data were modeled as normal distributions with the base-case value as the mean. The difference between high and low CMS and FSS values were used to approximate the standard deviation [34,37,38].

Utilities for the Outcomes

Model utilities were measured in healthy day equivalents (HDEs) and were obtained from a study by Dranitsaris and Leung using the Time Trade-Off (TTO) method (Table 3) [39,40]. In this study, subjects were asked how many days of “optimal health” they considered being equivalent to the time spent in various health states including combinations of acute and delayed CINV. Mean HDEs were used in the base-case analysis. Incremental benefit was converted to quality-adjusted life-years (QALYs), by dividing the difference in the mean HDEs for each treatment by 365 to estimate the number of healthy year equivalents (HYEs) gained [41]. When the TTO method is used to elicit utilities, estimation of HYEs and QALYs utilize the same assumptions and yield theoretically identical results [42,43].

Sensitivity Analyses

Univariate sensitivity analyses were performed to explore the impact of varying all probabilities, utilities, and costs on the incremental cost-effectiveness of the aprepitant management strategies. Probabilities and utilities were varied over the ranges derived from their 95% confidence intervals. Costs were varied according to minimum and maximum allowable payments from CMS reimbursement rates for physician and laboratory services and minimum and maximum medication costs from the FSS [34].

A probabilistic sensitivity analysis was performed to assess the robustness of the findings in the base case and provide confidence ranges for the incremental cost and effectiveness of the treatment strategies. A Monte Carlo simulation used 10,000 samples drawn from

Table 2: Estimated costs of care

<table>
<thead>
<tr>
<th>Costs</th>
<th>Cost ($)</th>
<th>Range ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprepitant 125 mg tab</td>
<td>64.27</td>
<td>64.12–64.42</td>
</tr>
<tr>
<td>Aprepitant 80 mg tab</td>
<td>59.09</td>
<td>59.06–59.11</td>
</tr>
<tr>
<td>Ondansetron 32 mg IV</td>
<td>134.83</td>
<td>131.68–137.98</td>
</tr>
<tr>
<td>Dexamethasone 4 mg tab</td>
<td>0.08</td>
<td>0.06–0.11</td>
</tr>
<tr>
<td>Metoclopramide 10 mg tab</td>
<td>0.12</td>
<td>0.01–0.09</td>
</tr>
<tr>
<td>Ativan 1 mg tab</td>
<td>0.12</td>
<td>0.06–0.30</td>
</tr>
<tr>
<td>Clinic visit (CPT 99213)</td>
<td>36.18</td>
<td>32.10–59.49</td>
</tr>
<tr>
<td>Comprehensive metabolic panel (CPT 80053)</td>
<td>14.77</td>
<td>11.74–14.77</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen costs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard regimen*</td>
<td>136.19</td>
<td>132.48–139.45</td>
</tr>
<tr>
<td>Three-drug regimen†</td>
<td>318.02</td>
<td>314.49–321.46</td>
</tr>
<tr>
<td>Rescue treatment‡</td>
<td>58.15</td>
<td>45.87–110.26</td>
</tr>
</tbody>
</table>

*Standard regimen = Ondansetron 32 mg IV + (Dexamethasone 4 mg tab × 7).
†Three-drug Regimen = Aprepitant 125 mg tab + (Aprepitant 80 mg tab × 2) + Ondansetron 32 mg IV + (Dexamethasone 4 mg tab × 9).
‡Rescue Treatment = Clinic visit, Comprehensive metabolic panel + (Metoclopramide 10 mg tab × 30) + (Ativan 1 mg tab × 30).

Table 3: Utilities used in the model as measured in healthy day equivalents (HDEs)

<table>
<thead>
<tr>
<th>Health state</th>
<th>HDEs</th>
<th>Range (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both acute and delayed CINV</td>
<td>0.90</td>
<td>0.40–1.35</td>
</tr>
<tr>
<td>Acute CINV, no delayed CINV</td>
<td>3.00</td>
<td>2.55–3.40</td>
</tr>
<tr>
<td>No acute CINV, delayed CINV</td>
<td>1.55</td>
<td>1.10–2.05</td>
</tr>
<tr>
<td>No acute CINV or delayed CINV</td>
<td>4.30</td>
<td>3.95–4.65</td>
</tr>
<tr>
<td>Three-drug regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both acute and delayed CINV</td>
<td>0.75</td>
<td>0.25–1.20</td>
</tr>
<tr>
<td>Acute CINV, no delayed CINV</td>
<td>3.00</td>
<td>2.55–3.45</td>
</tr>
<tr>
<td>No acute CINV, delayed CINV</td>
<td>1.40</td>
<td>0.90–1.90</td>
</tr>
<tr>
<td>No acute CINV or delayed CINV</td>
<td>4.25</td>
<td>3.85–4.70</td>
</tr>
</tbody>
</table>

CI, confidence interval; CINV, chemotherapy-induced nausea and vomiting.
distributions of probabilities, utilities, and costs. This sampling procedure accounts for uncertainty in treatment outcomes and was beyond the number of samples where convergence occurred. Expected values and central 95% ranges were calculated for the incremental cost, effectiveness, and incremental cost-effectiveness ratio (ICER). A willingness-to-pay threshold of $50,000/QALY or less was used to define strategies that provide cost-effective utilization of resources in the US health-care system, as has been defined by other authors [44,45]. All analyses were conducted using TreeAge Pro 2005 (Williamstown, MA, USA).

Results

During the 5 months of chemotherapy, the three-drug treatment regimen provided patients with 2.47 additional HDEs at an incremental cost of $682 per patient as compared with the standard treatment arm, and the strategy of adding aprepitant only after CINV offered an additional 1.24 HDEs at an incremental cost of $289 per patient (Table 4). The resulting ICERs are $267/HDE ($97,429/QALY) for the 3-drug strategy and $264/HDE ($96,333/QALY) for the strategy of adding aprepitant after development of CINV. Table 4 compares costs and benefits for the treatment strategies under consideration.

Univariate sensitivity analyses are displayed in a tornado diagram (Fig. 2). In this diagram, each bar represents the impact of uncertainty in an individual variable on the ICER. No bars cross the $50,000/QALY threshold, indicating that wide variation of the estimates for cost, probability, and utility from those chosen in our base case do not alter the results of our analysis. Threshold values were calculated for each variable but were meaningful only for the cost variables. The threshold value indicates the value of an individual variable at which the use of aprepitant becomes $50,000/QALY or less. At a cost of $96 for all aprepitant doses given during a cycle of chemotherapy, the three-drug strategy is cost-effective. Similarly, the ICER associated with adding aprepitant after the onset of CINV is most sensitive to the cost of aprepitant. The cost of rescue treatment also strongly influenced the ICER. When rescue treatment costs more than $498, the three-drug strategy becomes cost-effective. For instance, if more than six doses of a 5-HT3 antagonist are administered in rescue treatment, adding aprepitant to prevent CINV is cost-effective.

The results of the probabilistic sensitivity analysis were plotted as an incremental cost-effectiveness scatterplot (Fig. 3) to show the distribution of 10,000 trials from the Monte Carlo simulation. Each trial point provides a comparison of the incremental costs and benefits of three-drug management to conventional care. For each comparison, parameters for both management strategies were simultaneously and randomly sampled from the probability, cost, and outcome distributions to account for uncertainty in the base-case parameter estimates. The points could fall in four quadrants, the first of which represents a scenario where the three-drug management strategy is both

![Figure 2](image-url) Figure 2 Tornado diagram of univariate analyses. CINV, chemotherapy-induced nausea and vomiting; QALY, quality-adjusted life-year.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost ($)</th>
<th>HDEs</th>
<th>QALYs</th>
<th>CE ratio ($)</th>
<th>ICER ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard regimen</td>
<td>711</td>
<td>11.93</td>
<td>0.033</td>
<td>21,545</td>
<td>—</td>
</tr>
<tr>
<td>Three-drug regimen</td>
<td>1393</td>
<td>14.40</td>
<td>0.040</td>
<td>34,825</td>
<td>97,429</td>
</tr>
<tr>
<td>Add aprepitant after CINV</td>
<td>1000</td>
<td>13.17</td>
<td>0.036</td>
<td>27,778</td>
<td>96,333</td>
</tr>
</tbody>
</table>

QALY = HDE/365; CE ratio = Cost/QALY.

CINV, chemotherapy-induced nausea and vomiting.
more costly and more effective than the standard regimen. This quadrant contained 98.86% of the samples, all of which had an ICER of greater than $50,000/QALY. Quadrant II, where the three-drug strategy is more costly but less effective, contained only 1.14% of the samples. Quadrant III represents a situation where the triple-drug strategy is both less costly and less effective whereas quadrant IV represents a situation where the triple-drug treatment strategy is less costly and more effective. Neither quadrant III nor IV contained points. From the probabilistic sensitivity analysis, the ICER for the three-drug strategy was $100,516/QALY (95% confidence range $90,396/QALY-$111,239/QALY).

Conclusions

Although aprepitant use for prevention of CINV improves patient outcomes, the incremental benefit of the three-drug regimen is counterbalanced by the cost associated with this new agent. Using HDEs as a measure of quality of life, the addition of aprepitant offered a moderate gain in HDEs. When translated into QALYs, the ICER for aprepitant use exceeded $50,000/QALY with both strategies tested in our model and with wide variation in univariate and probabilistic sensitivity analyses. Routine use of aprepitant becomes cost-effective when the total cost of aprepitant for each cycle of chemotherapy is less than $96 (approximately $32 per dose). Although these costs are outside of the ranges used in the model, drug prices are potentially subject to greater flexibility than either utilities or probabilities and could be adjusted to achieve cost-effectiveness.

Assessing the cost-effectiveness of supportive care measures in oncology is necessary to ensure equitable allocation of resources given that the annual cost of caring for patients with cancer in the United States already exceeds $100bn [46]. Following the introduction of 5-HT3 antagonists for prevention of CINV, the cost-effectiveness of these agents was studied extensively. Several studies examining this issue found that these agents are cost-effective for prevention of CINV associated with both highly and moderately emetogenic chemotherapy [47–52]. These results likely reflect the dramatically increased efficacy of these agents for prevention of acute CINV when compared with the previous standard of care. Nevertheless, the cost-effectiveness of 5-HT3 antagonists for prevention of delayed CINV was recently assessed, and the use of these agents does not appear to be cost-effective beyond 24 hours after chemotherapy [53].

Economic evaluations provide important information regarding allocation of scarce resources and the desire to maximize economic efficiency [54]. A recent study by Dranitsaris and Leung demonstrated how decision analysis modeling can be used to estimate cost-effective pricing of new pharmaceuticals before they are introduced to the market [39]. This study found that at a cost of $CAN6.60 per dose, aprepitant would achieve economic efficiency relative to the Canadian health-care system using a threshold of $20,000/QALY to define “good value for money.” A separate willingness-to-pay analysis conducted in Canada, Spain, Italy, and Greece concluded that patients with cancer are willing to pay from $8 to $63 (US$ based on year 2000 exchange rates) per day for a 20% improvement in acute emesis and $9 to $50 per day for a 30% improvement in delayed emesis. This wide range represents significant differences in patient values between countries even after adjusted for socioeconomic variables and previous history of emesis [12].

The findings of our study provide important information regarding the role of the new NK-1 antagonist, aprepitant, in the overall management of cancer patients. Although the three-drug strategy provides only modest benefits for the prevention of CINV from a cost-effectiveness standpoint, its improved efficacy despite its high cost may be justified in the proper setting. In addition, the unit cost of aprepitant of approximately $60 used in our study is similar to what cancer patients in Western Europe were willing to pay for the increased efficacy of aprepitant, and the incremental cost of $682 represents a small fraction of the total cost of care for a patient receiving five cycles of chemotherapy. Moreover, the strategies analyzed in our study represent only two possible means of utilizing aprepitant to prevent CINV. It is likely that future studies will help define the role of this new anti-emetic agent for prevention of CINV. Our study indicates that parameters most likely to affect the cost-effectiveness of aprepitant include the cost of the medications, the likelihood of experiencing delayed CINV without treatment with an NK-1 antagonist, the likelihood of
experiencing acute CINV with and without treatment, and the benefits patients attribute to not having CINV.

Although our base-case model yielded an ICER of more than $50,000 per QALY, our sensitivity analyses indicate that aprepitant may be cost-effective in clinical environments where routine use of 5-HT3 antagonists as rescue medication is prevalent. In our model, prophylaxis with aprepitant is cost-effective in situations where 3 days of postchemotherapy ondansetron at a dose of 8 mg PO BID is used as rescue medication. Although there is substantial evidence that the addition of 5-HT3 antagonists to corticosteroids following the administration of highly emetogenic chemotherapy does not effectively improve prevention of delayed CINV, the use of 5-HT3 antagonists for rescue treatment appears to be widespread [55–60]. A recent study by Mertens et al. suggests that guidelines for the prevention of delayed CINV are not widely followed. In this study, only 25% of chemotherapy administrations of moderately or highly emetogenic potential received postchemotherapy corticosteroids. In contrast, 52% of these chemotherapy administrations received postchemotherapy 5-HT3 antagonists. Among patients receiving cisplatin, 23% received 5-HT3 antagonists but none were prescribed concurrent dexamethasone [60]. Thus, the use of aprepitant could be cost-effective if the addition of this agent reduces ineffective prescribing of 5-HT3 antagonists for the control of delayed CINV.

Several limitations of this study must be addressed. First, all probabilities and utilities used to populate the model are estimates derived from the literature. Each of these estimates carries inherent uncertainty. Possible selection bias associated with utilizing data from a single clinical trial as well as differences between the clinical trial setting and actual clinical use may impact our base-case effectiveness and resource use estimates by either over or underestimating our base-case model parameters. Nevertheless, both univariate and probabilistic sensitivity analyses were performed to address uncertainty in parameter estimates by exploring variability in each probability, cost, and outcome estimate. These analyses and an alternative structure for the model (aprepitant use after CINV occurs) addressed parameter and structural uncertainty in the model. Of note, utilities were specific to each strategy. Our results are maintained even when a single set of utilities is applied to all strategies. Second, the standard regimen used in this study did not include combination therapy for the prevention of delayed CINV. The combination of metoclopramide and dexamethasone may represent a more accepted strategy than dexamethasone alone [61]. Nevertheless, the additional efficacy of dexamethasone plus metoclopramide would bias the analysis toward the standard arm being more effective, which would make the aprepitant strategy appear even less cost-effective. It is likely that the enhanced effective-ness of dexamethasone plus metoclopramide was contained in the ranges explored in our sensitivity analyses. Third, it is possible that the costs of rescue treatment were underestimated if patients who experienced CINV required more aggressive intervention. Nevertheless, a recent study by Ihbe-Heffinger et al. showed that only 14% of patients who experience CINV required outpatient physician visits and only 0.5% required hospitalization [62]. Fourth, indirect costs such as time lost in usual activities were not considered. In the same study, 11.4% of patients with CINV lost workdays or required extra help at home as a result of their symptoms. The inclusion of such costs might improve the cost-effectiveness of aprepitant.

Although our study modeled ondansetron at a dose of 32 mg IV, several studies show that the dose of ondansetron can be lowered to 8 mg rather than 32 mg without loss of efficacy [63–65]. Additional studies indicate that the oral route of administration is equally as efficacious as the intravenous route [66,67]. Although the total cost of CINV prevention would be lowered by these adjustments, this change would affect all strategies equally, and the ICER would therefore remain unchanged. For example, at a cost of $33.71 for an 8-mg IV dose of ondansetron, the total cost of the three-drug regimen over five cycles of chemotherapy was $991 compared with $1393 for a 32-mg IV dose of ondansetron. The resulting ICERs were $286/HDE ($97,714/QALY) for the three-drug regimen and $266/HDE ($97,000/QALY) for the strategy of adding aprepitant after development of CINV when the cost of an 8-mg IV dose was used in the model.

An additional issue is that costs derived from CMS and FSS data may differ from other payer sources. Nevertheless, Medicare reimbursement data may provide the best estimate of direct medical care costs, because many public and private organizations use Medicare reimbursement methodology to set reimbursement rates [34]. The FSS is a program utilized by the Department of Veteran Affairs, Department of Defense, Public Health Service, Coast Guard, and Indian Health Service to obtain the best possible price for pharmaceuticals by negotiating for equal to or better than Most Favored Commercial Customer prices [36]. Although these sources may result in an underestimate of the true costs, this error would influence all strategies. Finally, although $50,000/QALY is a commonly applied metric of assessing the cost-effectiveness of health-care interventions in the United States [44,45], this is an arbitrary threshold. The cost-effectiveness threshold of $50,000/QALY was defined in the 1970s based on the cost of providing treatment for patients with end-stage renal disease. The cost of this service is now thought to exceed $120,000/QALY [68]. The results of our study indicate that the routine use of aprepitant at a cost of $97,429/QALY exceeds the accepted $50,000/QALY.
threshold but may be acceptable at a higher cost-effectiveness threshold.

Despite these limitations, our study suggests that the use of aprepitant for prevention of CINV associated with highly emetogenic chemotherapy provides benefits for preventing CINV at a current cost of the three-drug regimen that exceeds the common threshold for cost-effectiveness. Nevertheless, in clinical environments, where the risk of delayed CINV is high or the strategies for rescue treatment are costly, routine aprepitant use may be cost-effective. Targeting high-risk populations and understanding how actual CINV prevention differs from guideline recommendations will likely be necessary to identify other cost-effective uses for aprepitant until the cost of the medication is reduced.

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