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Analysis of Cumulative Probabilities Shows That the Efficacy of 5HT$_3$ Antagonist Prophylaxis Is Not Maintained

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**Purpose:** Several investigators have reported that the efficacy of 5HT$_3$ receptor antagonists is maintained over repeated cycles of chemotherapy. These investigators presented conditional probabilities of protection. Because conditional analyses by definition only include patients with protection in previous cycles, the results are flattened.

**Patients and Methods:** We applied a novel statistical approach to investigate whether the efficacy of the 5HT$_3$ receptor antagonist ICS 205-930 (tropisetron) is maintained over repeated cycles of weekly high-dose cisplatin. Overall protection was determined based on cumulative probabilities with the Kaplan-Meier method. Complete protection was calculated with a three state model for transitional probabilities. Eighty-three patients were studied.

**Results:** Over six consecutive cycles, protection against both acute and delayed emesis decreased significantly. The initial complete and overall protection rates against acute emesis of 71% and 95%, respectively, decreased to 43% and 72% in the sixth cycle of chemotherapy. Similarly, the protection rates of 31% and 68% against delayed emesis decreased to 6% and 40%, respectively.

**Conclusion:** We conclude that overall and complete long-term protection is more accurately measured by cumulative probabilities then with a method that is based on conditional probabilities. Our statistical approach shows that the efficacy of 5HT$_3$ antagonists is not maintained.


To avoid this, we applied the Kaplan-Meier method and introduced a three-state model for transitional probabilities. These statistical tools were used to investigate the efficacy of the 5HT$_3$ antagonist ICS 205-930 (tropisetron) over multiple cycles of weekly high-dose cisplatin. Because it is well known that 5HT$_3$ antagonists do not properly control delayed emesis, we analyzed the effect on acute and delayed nausea and vomiting separately.

**Patients and Methods**

Patients were treated in the framework of two prospective phase II studies. One was designed for patients with head and neck cancer who received single-agent cisplatin 80 mg/m$^2$ weekly for 6 weeks. The other was for patients with non-small-cell lung cancer, melanoma, cancer of unknown primary, and mesothelioma who received cisplatin 70 mg/m$^2$ weekly on weeks 1, 2, 3, 5, 6, and 7, with etoside 50 mg orally days 1 through 15 and 29 through 43.

Eligibility criteria required the following: no previous chemotherapy; World Health Organization (WHO) performance status $\leq 2$; leukocyte count greater than 3,000/μL; platelet count greater than 75,000/μL; serum creatinine level less than 120 μmol/L or creatinine clearance greater than 60 mL/min; and bilirubin level less than 25 μmol/L. Exclusion criteria were the use of drugs that can influence nausea, vomiting, or diarrhea, such as corticosteroids, other antiemetics, narcotics (unless chronically administered), or benzodiazepines (except small doses given as sleeping medication). Also excluded were patients with preexistent nausea and/or vomiting, brain metastases or leptomeningeal involvement, and alcohol abuse (more than 3 U/d).

The chemotherapy protocols did not allow for chemotherapy dose reductions. If at scheduled retreatment leukocyte count was less than 2,500/μL and/or platelet count was less than 75,000/μL, treatment was postponed until recovery. In case of treatment delay of more than 2 weeks or the occurrence of neurotoxicity or renal toxicity
greater than grade 1, the patient was taken off study. Informed consent was obtained from all patients.

Cisplatin was administered in 3% hypertonic saline over 3 hours, preceded by 1,000 mL of dextrose saline over 4 hours, and followed by 2,000 mL dextrose saline over 8 hours. Tropisetron 5 mg intravenously (IV) was administered over 15 minutes just before the infusion of cisplatin, followed by a daily oral dose of 5 mg before breakfast on days 2 through 5.12

Efficacy parameters for tropisetron were nausea and vomiting. The duration of nausea and the number of retches and vomits were recorded daily by nursing charts during the first 24 hours and by patient diary cards during days 1 through 5. The following definitions were used: complete protection, no nausea and vomiting; partial protection, one to four retches or dry retches and/or ≤ 4 hours nausea; overall protection, the sum of complete and partial protection; protection failure, more than four retches and/or more than 4 hours nausea; withdrawal, drop-out for reasons other than antiemetic treatment failure, eg, discontinuation of chemotherapy because tumor progression, decline in performance status, toxicity other than nausea and vomiting, the first prescription or an increase in the dosages of narcotic analgesics or benzodiazepines, and incomplete follow-up.

Patients with protection failure on day 1 were not eligible for further tropisetron treatment and were taken off study. Patients who experienced failure during days 2 through 5, but with complete or partial protection on day 1, continued tropisetron in subsequent cycles during day 1, until protection failure occurred. The decision to withdraw or censor was made either at the completion of the first 24 hours (acute emesis) or at the protocol date of the next cycle (delayed emesis). Patients who were withdrawn after completion of the first 24 hours were available for the acute emesis protection evaluation.

Written informed consent was obtained from all patients, and the study was conducted according to the guidelines of the institutional review boards.

**Statistical Analysis**

The primary aim was to accurately determine overall protection against acute emesis over a total of six chemotherapy cycles. It was required that the SE of overall protection in cycle six should be ≤ 7%. Assuming a constant overall protection rate of 80% in each cycle, a total of 100 patients in the first cycle would result in approximately 33 patients at the start of cycle six. With 33 patients, the SE of a rate of 80% is 7%. Consequently, approximately 100 patients were planned to enter onto the study. Acute and delayed emesis were analyzed separately with overall and complete protection as end points. For delayed emesis (days 2 through 5), a worst day analysis was used because this is the most realistic approach to measure protection for the entire 4-day period over multiple cycles of chemotherapy.

Cumulative protection of overall protection over multiple cycles was calculated with the Kaplan-Meier method,13 where protection failure was the end point. The calculations were derived from product and addition rules for probabilities and Bayes theorem.14 Confidence intervals of overall protection were calculated with Greenwood's formula.15

A realistic analysis of complete protection is complicated because of the possible transitions between three states (complete protection, partial protection, and protection failure); a situation for which the Kaplan-Meier analysis is unsuitable. Therefore, we applied a three-state Markov model for transitional probabilities, where transitional probabilities are independent of the results in prior states, and in which the transitional probabilities vary over time.16 Transitional probabilities were estimated from simple tabulations. The probability of complete protection in a given cycle follows from the sum of the products of transitional and state probabilities in previous cycles. SEs and confidence intervals of complete protection in this model were calculated with a bootstrap technique (see Appendix).

**RESULTS**

Between January 1992 and July 1993, 83 eligible patients were entered onto the study. Patient characteristics are listed in Table 1. The majority of patients were male, which can be attributed to the male preponderance of the selected tumors.

All patients were assessable for at least the first 24 hours of the first cycle of chemotherapy. A total of 278 cycles of IV tropisetron on day 1 and 209 cycles of oral tropisetron on days 2 through 5 were administered. Table 2 lists the number of assessable patients per cycle and the number of patients who were taken off study in subsequent cycles for non-cause-specific reasons. The reasons for withdrawal are listed in Table 3. To date, eight patients were dropped from the study because of delayed emesis protection failure despite protection on day 1. Because these patients, in point of fact, had protection against acute emesis, they are included in the analysis as such, and considered as withdrawals in subsequent cycles.

In the delayed protection analysis, 75 patients were included. Two patients did not receive tropisetron on days 2 through 5 because they had protection failure on day 1 of the first cycle, and six others were not assessable in the first cycle because of incomplete follow-up (three patients), prescription of benzodiazepines (one patient), and no intake of tropisetron (two patients). Five patients

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
<th>No. of Patients (N = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>55</td>
</tr>
<tr>
<td>Range</td>
<td>30-72</td>
</tr>
<tr>
<td>Male/female</td>
<td>63/20</td>
</tr>
<tr>
<td>WHO performance status</td>
<td>1</td>
</tr>
<tr>
<td>Median</td>
<td>0-2</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>36</td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>16</td>
</tr>
<tr>
<td>Melanoma</td>
<td>9</td>
</tr>
<tr>
<td>Cancer unknown primary</td>
<td>8</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>12</td>
</tr>
<tr>
<td>Cervical carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Cisplatin 60 mg/m²</td>
<td>36</td>
</tr>
<tr>
<td>Cisplatin 70 mg/m² + etoposide 50 mg</td>
<td>47</td>
</tr>
</tbody>
</table>
Table 2. Assessable and Withdrawn Patients Per Cycle

<table>
<thead>
<tr>
<th>Cycle</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>No. of patients</td>
<td>83</td>
<td>61</td>
<td>49</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Withdrawals</td>
<td>18</td>
<td>8</td>
<td>10</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Days 2-5</td>
<td>No. of patients</td>
<td>75</td>
<td>41</td>
<td>33</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Withdrawals</td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

developed protection failure against acute emesis during subsequent cycles and were included as withdrawals in the delayed protection analysis.

Figure 1 shows the overall protection rates and 95% confidence limits for acute and delayed emesis. Figure 2 shows this information for complete protection. It can be seen from these figures that the complete and overall protection rates for delayed emesis are lower than for acute emesis, and that these rates decrease significantly over the treatment period of six cycles. To date, initial complete and overall protection rates against acute emesis of 71% and 95%, respectively, decreased to 43% and 72%, and the protection rates against delayed emesis of 31% and 68%, respectively, decreased to 6% and 40%. The SE of overall protection in cycle six was 0.046. As an example of the calculation of protection during the six cycles, Table A1 in the Appendix gives the distribution of protection for acute emesis; the text in the Appendix also provides the calculation of protection rates for acute emesis for both cumulative and conditional rates.

Protection failures regarding delayed emesis were mainly observed on days 2 and 3. Using a worst-day analysis, the complete protection rate during days 2 through 5 of the first cycle was as low as 31% (Fig 2). However, when a day-by-day analysis was used, the protection rates in the first cycle were 40%, 61%, 78%, and 84% for days 2, 3, 4, and 5, respectively. A similar pattern was observed in the subsequent cycles (data not shown).

Median age, sex, and chemotherapy protocol were analyzed in relationship to overall protection. Only age was found to have a borderline significant influence on the overall protection on day 1; we observed that younger patients were less well protected ($P = .04$). Sex ($P = .84$) and chemotherapy protocol ($P = .34$) were not significant variables.

**DISCUSSION**

Virtually all clinical investigations with 5HT$_3$ antagonists have focused on chemotherapy-naive pa-
Efficacy of 5HT₃ Antagonist Prophylaxis Not Maintained

Patients who were either studied in the first chemotherapy cycle only, or included in a cross-over design for the first two cycles of chemotherapy. The issue of effectiveness of these antiemetics over multiple cycles has been inadequately addressed.

Decreasing efficacy has been demonstrated with the use of conventional antiemetic agents during consecutive cycles of both cisplatin- and non–cisplatin-containing chemotherapy.¹⁷,¹⁸ Few data exist on the sustainment of efficacy of 5HT₃ antagonists. One study of ondansetron over six cycles of non-cisplatin-containing chemotherapy suggested decreasing protection.¹⁷ Recently, the Italian Group for Antiemetic Research¹⁹ reported that the efficacy of the combination of ondansetron and dexamethasone was maintained during three cycles of cisplatin chemotherapy, whereas the efficacy of a metoclopramide combination was not maintained. In their analysis, only patients who were able to complete all three cycles of chemotherapy were included. Of note, these investigators clearly demonstrated that the protection obtained in previous chemotherapy cycles is the most important prognostic factor for sustainment of efficacy.

In 1992 and 1993, three independent investigators reported that the antiemetic efficacy of 5HT₃ receptor antagonists was maintained after multiple cycles of chemotherapy.¹⁵,¹⁷,¹⁸ In these studies, approximately one third of the patients were treated with cisplatin chemotherapy regimens at conventional 3- to 4-week intervals. These investigators used the method of conditional probabilities of protection for their analyses. By definition, this type of analysis includes only patients who are protected in previous cycles, which leads to selection of favorable patients and therefore to an overestimation of the sustainment of protection. This bias can be avoided with the calculation of cumulative probabilities, including all protection failures in the sum of failures during subsequent cycles, and incorporating censoring of the data due to non-cause-specific withdrawals in previous cycles.

We have investigated the efficacy of the 5HT₃ antagonist tropisetron over multiple cycles of chemotherapy with the Kaplan-Meier method for the measurement of overall protection and with a three-state model for transitional probabilities for the calculation of cumulative protection.

Using these methods, we found that protection against both acute and delayed emesis decreased significantly. Initial complete and overall protection rates against acute emesis were 71% and 95%, respectively, and decreased to 43% and 72%. The protection rates against delayed emesis of 31% and 68%, respectively, decreased to 6% and 40%.

To illustrate the difference in outcome of the two methods of analysis, Fig 3 shows both the conditional and cumulative protection rates for acute emesis. It can be seen that the conditional analysis flatters the results.

Our findings that tropisetron was substantially less protective against delayed nausea and vomiting are in accord with previous reports, indicating that 5HT₃ antagonists do not properly control delayed emesis.²⁰,²² However, the low complete protection rate of 31% in the first cycle is partly because of our use of a worst-day analysis instead of a day-by-day analysis. Because the primary aim of our study was to investigate whether the efficacy of a 5HT₃ antagonist is maintained over multiple cycles of chemotherapy, we applied the worst-day analysis.

We conclude that the Kaplan-Meier method for the measurement of overall protection and the three-state model for transitional probabilities for the measurement of complete protection are the proper methods to analyze accurately the efficacy of antiemetics over multiple cycles of chemotherapy. This approach shows that the efficacy of initially highly effective 5HT₃ receptor antagonist prophylaxis is not maintained.

Fig 3. Difference in protection against acute emesis related to the conditional versus cumulative calculation method.
APPENDIX

The overall accounting of patients is given in the equation:

\[ N_{i+1} = N_i - F_i - W_i \]

where \( N_{i+1} \) is the number entering cycle \( i + 1 \); \( N_i \) is the number entering cycle \( i \); \( F_i \) is the number of protection failures in cycle \( i \); and \( W_i \) is the number of withdrawals after cycle \( i \) prior to cycle \( i + 1 \). (For example, \( N_1 = N_1 - F_1 - W_1 : 61 = 83 - 4 - 18 \).

Table A1. Distribution of Protection for Acute Emesis During Six Cycles

<table>
<thead>
<tr>
<th>Cycle 1:</th>
<th>cycle 1</th>
<th>Cycle 4:</th>
<th>cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP</td>
<td>PP</td>
<td>PF</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 2:</td>
<td>cycle 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CP</td>
<td>PP</td>
<td>PF</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Cycle 3:</td>
<td>cycle 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CP</td>
<td>PP</td>
<td>PF</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: CP, complete protection; PP, partial protection; PF, protection failure.

**CALCULATION OF CUMULATIVE PROTECTION RATES WITH THE KAPLAN-MEIER METHOD**

For the calculation of cumulative protection rates with the Kaplan-Meier method, two variables are defined for each patient: when no protection failure occurs in cycles one to six, and when protection failure occurs in one of the cycles one to six. Time one, two to six is the cycle number when protection failure occurs or last cycle number of follow-up.

Calculation of the conditional protection rates and the cumulative protection rates with the Kaplan-Meier method for acute emesis is as follows:

**Cycle 1:**

\[ P(\text{OP}) = \frac{59 + 20}{83} = 0.95 \]

**Cycle 2:**

Conditional:

\[ P(\text{OP cycle 2 } | \text{ OP in cycle 1}) = \frac{42 + 15}{61} = 0.93 \]

Cumulative:

\[ P(\text{OP in cycle 2}) = P(\text{OP in cycle 2 } | \text{ OP in cycle 1}) \times P(\text{OP in cycle 1}) = (0.93)(0.95) = 0.88 \]

**Cycle 3:**

Conditional:

\[ P(\text{OP in cycle 3 } | \text{ OP in cycle 2}) = \frac{34 + 12}{49} = 0.94 \]
Cumulative:
P(\text{OP in cycle 3}) = 
= P(\text{OP in cycle 3 | OP in cycle 2}) \times P(\text{OP in cycle 2}) = 
= (0.94) (0.88) = 0.83

Analogously:
Cycle 4: conditional: (22 + 11)/36 = 0.92
cumulative: (0.92) (0.83) = 0.76
Cycle 5: conditional: (16 + 11)/27 = 1.0
cumulative (1.0) (0.76) = 0.76
Cycle 6: conditional: (13 + 8)/22 = 0.95
cumulative: (0.95) (0.76) = 0.72

CALCULATION OF COMPLETE PROTECTION RATES USING A TRANSITIONAL-PROBABILITY MODEL

For each cycle, three different states can be distinguished: complete protection (CP), partial protection (PP), and protection failure (PF). PF is a so-called "absorbing state": once reached it cannot be left because the patient goes off study. A CP or PP can change either to a CP, or to a PP or a PF in the next cycle. Between two states in two consecutive cycles, the transition-probability can easily be estimated from a cross-table.

The transitional probabilities are as follows (i = 1, 2, 3, 4, 5):

\[ P(\text{CP, } | \text{ CP}) \]
\[ P(\text{CP, } | \text{ PP}) \]
\[ P(\text{CP, } | \text{ PF}) = 0 \]
\[ P(\text{PP, } | \text{ CP}) \]
\[ P(\text{PP, } | \text{ PP}) \]
\[ P(\text{PP, } | \text{ PF}) = 0 \]
\[ P(\text{PF, } | \text{ CP}) = 1 - P(\text{CP, } | \text{ CP}) - P(\text{PP, } | \text{ CP}) \]
\[ P(\text{PF, } | \text{ PP}) = 1 - P(\text{CP, } | \text{ PP}) - P(\text{PP, } | \text{ PP}) \]
\[ P(\text{PF, } | \text{ PF}) = 1 \]

The state probabilities in cycle one are (# denotes number):

\[ P(\text{CP}) = \frac{\#\text{CP in cycle 1}}{\#\text{treated patients in cycle 1}} \]
\[ P(\text{PP}) = \frac{\#\text{PP in cycle 1}}{\#\text{treated patients in cycle 1}} \]
From these probabilities and the transition probabilities the protection rates are calculated as follows:

\[
P(CP_{i+1}) = P(CP_i) P(CP_{i+1} | CP_i) + P(PP_i) P(CP_{i+1} | PP_i)
\]

\[
P(PP_{i+1}) = P(CP_i) P(PP_{i+1} | CP_i) + P(PP_i) P(PP_{i+1} | PP_i)
\]

\[
P(PF_{i+1}) = 1 - P(CP_{i+1}) - P(PP_{i+1})
\]

Application of these formulas to the data for acute emesis gives the following results:

**Cycle 1:**

- \( P(CP) = \frac{59}{83} = 0.71 \)
- \( P(PP) = \frac{20}{83} = 0.24 \)

**Cycle 2:**

- Conditional protection probabilities:
  - \( P(CP\text{ in cycle 2} | CP\text{ in cycle 1}) = \frac{36}{46} = 0.78 \)
  - \( P(CP\text{ in cycle 2} | PP\text{ in cycle 1}) = \frac{6}{15} = 0.40 \)
  - \( P(PP\text{ in cycle 2} | CP\text{ in cycle 1}) = \frac{8}{46} = 0.17 \)
  - \( P(PP\text{ in cycle 2} | PP\text{ in cycle 1}) = \frac{7}{15} = 0.47 \)

- Cumulative probabilities:
  - \( P(CP\text{ in cycle 2}) = (0.78) (0.71) + (0.40) (0.24) = 0.65 \)
  - \( P(PP\text{ in cycle 2}) = (0.17) (0.71) + (0.47) (0.24) = 0.23 \)

Calculations for cycles three through six are analogous and summarized in the following table:

<table>
<thead>
<tr>
<th>cycle i</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P(CP_i) )</td>
<td>0.71</td>
<td>0.65</td>
<td>0.60</td>
<td>0.49</td>
<td>0.44</td>
<td>0.43</td>
</tr>
<tr>
<td>( P(PP_i) )</td>
<td>0.24</td>
<td>0.23</td>
<td>0.22</td>
<td>0.27</td>
<td>0.32</td>
<td>0.29</td>
</tr>
<tr>
<td>( P(CP_{i+1}</td>
<td>CP_i) )</td>
<td>0.78</td>
<td>0.76</td>
<td>0.74</td>
<td>0.89</td>
<td>0.71</td>
</tr>
<tr>
<td>( P(CP_{i+1}</td>
<td>PP_i) )</td>
<td>0.40</td>
<td>0.46</td>
<td>0.22</td>
<td>0</td>
<td>0.37</td>
</tr>
<tr>
<td>( P(PP_{i+1}</td>
<td>CP_i) )</td>
<td>0.17</td>
<td>0.18</td>
<td>0.19</td>
<td>0.11</td>
<td>0.29</td>
</tr>
<tr>
<td>( P(PP_{i+1}</td>
<td>PP_i) )</td>
<td>0.47</td>
<td>0.46</td>
<td>0.67</td>
<td>1.00</td>
<td>0.50</td>
</tr>
</tbody>
</table>

The SEs and confidence intervals of complete protection, \( P(CP_i), i = 1, 2, \ldots, 6 \) are calculated with the bootstrap method, in particular using the data resampling approach. Two thousand bootstrap samples were generated; each bootstrap sample was generated with replacement from the empirical distribution of the data and was of the same size as the original dataset. A 95% bootstrap-percentile confidence interval finally follows from:

\[
P(\hat{CP}) - \{P_{2.5\%}(\hat{CP}) - P(CP_i)\} < P(CP_i) < P(\hat{CP}) - \{P_{97.5\%}(\hat{CP}) - P(CP_i)\}
\]

where \( P(\hat{CP}) \) is the bootstrap estimator for \( P(CP_i) \) and \( P_{2.5\%}(\hat{CP}) \) and \( P_{97.5\%}(\hat{CP}) \) are the 2.5th and 97.5th percentile of the 2,000 bootstrap sample distribution of \( P(\hat{CP}) \).
REFERENCES


