Phase II Trial Testing the Antiemetic Efficacy of a Single-Day Low Dose of Aprepitant (or Fosaprepitant) added to a 5-HT_3 Receptor Antagonist plus Dexamethasone in Patients Receiving Carboplatin

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Background

Chemotherapy-induced nausea and vomiting (CINV) is consistently listed as one of the greatest concerns of patients with cancer, negatively affects quality of life (QOL) and is a leading cause of increasing use of health care resources including urgent care visits (1).

Major risk factors increasing the likelihood of emesis with chemotherapy include: female gender, young age, and low chronic alcohol use. It should be noted; however, that the main predictive factor for the development of CINV is the emetic potential of a given chemotherapeutic agent (1).

Carboplatin causes both acute and delayed emesis. Results from 4 recent randomized clinical trials (as in table 1) have shown that the rate of emesis, even with two agent antiemetic regimens, with carboplatin is higher than was previously recognized. Guideline groups have typically classified this agent as moderately emetic (MEC); however, its risk of inducing vomiting is at the upper range of this classification, and borders on highly emetic (2,3). The recommendation for prevention has been the use of a two-drug regimen (a 5hydroxytryptamine receptor antagonist (5-HT_3RA) plus dexamethasone). Based on the evidence from the 4 recent trials mentioned below, guideline groups are considering recommending the addition of a neurokinin-1 receptor antagonist (NK_1RA) in all patients receiving carboplatin, using traditional NK_1RA dosing and schedules.

The recent randomized studies have shown that patients given only a 2-drug regimen have about a 50% likelihood of emesis if they are women, and about a 30% likelihood of emesis if they are men. Major improvements were reported when a neurokinin-1 receptor antagonist (NK_1RA) aprepitant was added (4,5,6,7), as seen in table 1. This improvement is of a similar magnitude to that seen in patients receiving cisplatin (a chemotherapeutic agent for which a 3 drug regimen containing an NK_1RA is universally guideline-recommended). Similar improvements were also seen in a trial in which the NK_1RA antiemetic was rolapitant rather than aprepitant (8). The Tanioka and Yahata studies were conducted entirely in patients with GYN malignancies, and it is not surprising that the control rates are lower in these all female groups; nonetheless, the magnitude of benefit with the addition of the 3rd agent is similar in both genders.

Table 1. Complete Emetic Control rate of 3-drug NK_1RA-containing regimen over 2-drug regimen in randomized trials in patients receiving carboplatin (4,5,6,7)

Overall (0-120 hours) Complete response	NK_1RA + 5-HT3RA +DEX	$5\text{-}HT_3RA$ +DEX	Absolute difference
Tanioka (N=91) *	62%	52%	10%
Ito (N=134)	80%	67%	13%
Yahata (N=324) *	62%	47%	15%
Gralla (N=192)	84%	70%	14%

* Studies conducted in women only

The most commonly used neurokinin-1 receptor antagonist, aprepitant, is generally given over 3 days. Interestingly, most studies indicate that this class of agent gives similar results when given in just one day, or over multiple days (9). Typically the 1 day regimens use higher NK_1RA doses (such as 150 mg of IV fosaprepitant or 165 mg of oral aprepitant), although a dose response relationship has not been clearly established for this purpose. Recent studies conducted by Roila compared the efficacy of aprepitant on one day at a low dose (125 mg) versus the full three day regimen totaling 285 mg (10, 11) in patients receiving either cisplatin or the combination of anthracyclines plus cyclophosphamide (AC). In both double-blind studies, those patients randomly assigned to just one day of lower dose aprepitant had control of emesis equal to those receiving multiple days and higher total doses. In both of these trials, patients assigned to the single day aprepitant arm also received additional antiemetics on days 2 and 3. However, recent studies have failed to show an advantage for continuing dexamethasone after day 1 in patients receiving AC (14) or in those receiving cisplatin (15). Additionally, a meta-analysis (16) indicated that as long as dexamethasone is given on day 1, there is no advantage to adding a serotonin antagonist (such as ondansetron) after day 1, and ondansetron has been shown to be similar to metoclopramide in the delayed emesis phase. Similarly to studies conducted by Roila (10, 11), Grunberg and colleagues showed noninferiority of single-dose intravenous (IV) fosaprepitant (a phosphorylated analog of aprepitant that is rapidly converted to aprepitant after IV administration) in a randomized study involving over 2000 patients receiving cisplatin chemotherapy (12). Fosaprepitant 115 mg IV has been approved as an alternative to the 125-mg oral aprepitant dose on day 1 of a 3-day regimen (13).

The role of continued steroids after day 1 in patients receiving carboplatin has only been recently tested, and this has been part of the trials using a variety of chemotherapeutic agents.

Although current guidelines often recommend the use of dexamethasone on 3 consecutive days after MEC, there are several newer considerations that call this into question: 1) a recently published meta-analysis of RCTs comparing 1-day versus 3-day duration of dexamethasone for the CINV prophylaxis, showed that 1-day therapy provides similar efficacy in control (18). Many of these patients received carboplatin. Of note also, a Japanese study conducted in 402 patients receiving either AC or Cisplatin (HEC) showed no difference in antiemetic efficacy (non-inferiority) of a single day dexamethasone regimen when prospectively compared with a 3 day dexamethasone regimen. Importantly, the 1 day regimen found significant reductions in steroid induced side effects (15). Additionally, a large multinational trial in patients receiving AC chemotherapy showed that a single dose of dexamethasone on day 1 along with a single day of NEPA (combination of 5-HT_3RA palonosetron with NK_1RA netupitant) offers convenient single-day prophylaxis for both acute and delayed CINV (17), with competitive antiemetic efficacy when compared with historical experiences. 2) Carboplatin is no longer considered to be "MEC" by some guideline groups (MASCC / ESMO).

Lower dose regimens and those of a shorter duration, not only are less expensive, but also are the easiest possible regimen for the patient to adhere to, making antiemetic regimens very easy. These shorter regimens are also easier to order, making compliance with evidence-based guidelines more likely. Additionally, with a shorter administration schedule, there is less chance of drug-drug interactions and side effects. All studies indicate that oral and IV antiemetics of these classes are equally efficacious (12).

All three classes of agents used in this trial have been commercially available for more than a decade and have been used many million times. The serotonin antagonist ondansetron was approved more than 2 decades ago. Its major side effects are mild headache and mild constipation, both of which are easily treated, if desired by common laxatives or acetaminophen. While intravenous ondansetron is associated with mild QTc prolongation, when given orally at the dose in this study, QTc prolongation is trivial, and the FDA has not asked for any additional warnings for such oral dosing. Agents of this class also can give mild increases in transaminases, of no known clinical significance. Other agents in this class, such as palonosetron have similar side effects to ondansetron. Aprepitant has few recognizable side effects in comparative clinical trials. It may be associated with increased hiccoughs, although this effect is seen only in men. The intravenous pro-drug form of aprepitant, fosaprepitant, has similar efficacy, pharmacokinetics, and side effects when compared with aprepitant (12). However, fosaprepitant is associated with an increased risk of venous irritation, when compared with the oral agent; this effect is greatest when given with AC chemotherapy and least when given with platinum agents (as in this protocol). Both these NK1RAs have a mild effect on CYP 3A4. This effect prolongs the half-life of dexamethasone, which is seen as an advantage in this trial, perhaps prolonging its beneficial effects. The side effects of dexamethasone are well known and include hyperglycemia and mood changes. As this protocol decreases the exposure to dexamethasone over some guidelines, it is expected that there may

be fewer corticosteroid adverse effects for patients on this protocol than for those who are placed on NCCN guideline recommended regimens.

Guideline groups are now starting to recommend a 3-agent preventive antiemetic regimen for patients receiving carboplatin, based on the evidence from the studies presented in table 1; however, not all guideline groups have yet made this recommendation. If it can be shown that a less expensive, more convenient (1-time administration), and potentially safer regimen performs in the same way for patients receiving carboplatin as it did for those receiving cisplatin or AC chemotherapy, and similarly to those receiving 3 days of aprepitant with carboplatin in the recent randomized trials, a new standard may be established.

Objectives

- Primary: To determine in patients receiving their first cycle of carboplatin-based chemotherapy, the complete control rate of emesis (acute and delayed; no vomiting and no use of rescue medications) with the addition of one dose of the oral aprepitant or intravenous fosaprepitant to a combination of oral dexamethasone + an oral 5-HT_3RA (ondansetron).
- Secondary: To estimate the control rate on the second cycle of this chemotherapy in those patients agreeing to be assessed in the subsequent chemotherapy cycle.

Methods

Assessment

CINV will be assessed by using the validated MASCC Antiemesis Tool (MAT) (19), which efficiently and accurately evaluates the incidence of vomiting and the severity of nausea and vomiting in the acute and delayed emesis periods.

Patients will be enrolled at Jacobi Medical Center and Montefiore Medical Center. Patients will be asked to sign an informed consent form. Patients will be called on day 2 and 5 to remind about form completion and will return the MAT form on their next outpatient visit (or immediately after completion if the patient is an inpatient).

Consent forms then will be kept at a clinical trial center in a file. Case report forms were developed to capture data relevant to research.

Patient selection Inclusion criteria

- Age 18 and above
- No prior chemotherapy

- Confirmed malignancy, scheduled to receive carboplatin monotherapy, or carboplatin in combination with agents of minimal, low, or moderate emetic potential
- Laboratory parameters adequate for chemotherapy

Exclusion criteria

- Patients with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 3 or 4
- Presence of nausea and vomiting or use of major antiemetic agents during the 24 hours before chemotherapy administration
- Patients receiving radiotherapy within 5 days prior to the carboplatin
- Pregnancy or lactation
- Known allergy to any of the 3 antiemetics

Antiemetic Medication administration

All medications that will be used in this study are commercially available. NK1RA have been used for over 12 years and 5-HT3RA and dexamethasone have been used even longer than that. All common side effects of these medications were mentioned above and have also been captured in consent form. We are not expecting serious adverse events since these are commonly used agents that are almost never associated with SAEs, and we are giving a lower dose and frequency of these FDA approved medications. They may be obtained or dispensed either by the Jacobi Medical Center, or the Montefiore Medical Center pharmacies, or aprepitant may be obtained by prescription from an outside pharmacy. If aprepitant is obtained at an outside pharmacy, the patient will bring the agent to their chemotherapy appointment; all NK_1RA drug administration will be directly observed. The use of either aprepitant or fosaprepitant will be entirely the choice of the ordering oncologist, as both agents are equivalent (12).

Ideally all drugs will be given immediately before (within 5 minutes) chemotherapy; however if a delay occurs up to 2 hours between the antiemetics and chemotherapy, this will be allowable and no additional dosing will be needed. The time of administration of the NK_1RA in relation to the chemotherapy will be recorded.

All patients will be given 125 mg of aprepitant orally or 115 mg IV of fosaprepitant prior to the first cycle of carboplatin-based chemotherapy.

<u>Antiemetic drug doses and schedules (same doses in all age and gender groups).</u> Please see medication package inserts attached separately.

Aprepitant or Fosaprepitant:

- 125 mg of Aprepitant orally immediately prior to chemotherapy

- If fosaprepitant given instead, it will be administered immediately prior to chemotherapy at 115mg IV (over 20 minutes). The administration site of the fosaprepitant will be noted and will be evaluated for possible venous irritation.

  Dexamethasone:
- 20 mg of dexamethasone orally immediately prior to chemotherapy

  Ondansetron:
- 16 mg orally, immediately prior to the chemotherapy.

Table 2. Antiemetic Dosing and Schedule

Day 1 (immediately prior to chemotherapy, only)
- aprepitant 125mg po or fosaprepitant 115mg IV - ondansetron 16 mg po - dexamethasone 20mg po

CYCLE 2:

Patients agreeing to be followed on the second cycle with be assessed in the same way. During the follow-up visit after the first cycle, patients on study will be asked if they wish to continue participation during their second chemotherapy cycle (given that they are still eligible). Patients will not need to sign a separate consent, but will need to give their verbal affirmation, which will be noted in the case report form.

The dosing and timing of the antiemetics may change according to the results in the first cycle, and other demographic characteristics, as follows:

<u>Female patients:</u>

- If there was no vomiting on the first cycle and the antiemetics were well tolerated, all antiemetics will be given identically to cycle 1.

- If any vomiting was experienced on the first cycle, patients will instead receive the typical 3day aprepitant (125 mg po day 1, and 80 mg po days 2 and 3), or fosaprepitant 150 mg IV (given over 30 minutes) on day 1 only. (The choice of the aprepitant or fosaprepitant regimen will be at the discretion of the ordering oncologist). Ondansetron and dexamethasone on day 1 will be given as on cycle 1. In addition, 12mg of dexamethasone will be given on day 3.

<u>Male patients</u>:

- For those aged 50 or older, if there was no vomiting with the first cycle and the antiemetics were well tolerated, all antiemetics will be given identically to cycle 1 EXCEPT that the aprepitant dose will be reduced to one 80 mg oral administration on day 1. If fosaprepitant

is used, it will be given at a total dose of 75 mg over 15 minutes. All will be given immediately prior to chemotherapy. Ondansetron and dexamethasone will be given as with cycle 1.

- For those under age 50, if there was no vomiting on the first cycle and the antiemetics were well tolerated, all antiemetics will be given identically to cycle 1.

- Male patients of any age, if they experienced any vomiting on the first cycle, will instead receive the typical 3-day aprepitant (125 mg po day 1, and 80 mg po days 2 and 3), or fosaprepitant 150 mg IV (given over 30 minutes) on day 1 only. (The choice of the aprepitant or fosaprepitant regimen will be at the discretion of the ordering oncologist). Ondansetron and dexamethasone on day 1 will be given as on cycle 1. In addition, 12mg of dexamethasone will be given on day 3.

Statistics and Analysis:
The primary goal of the study is to estimate the complete control rate of emesis with the addition of one dose of the oral NK_1RA aprepitant or the IV NK_1RA fosaprepitant to a combination of oral dexamethasone + an oral 5-HT_3RA (ondansetron). We will compute the relevant proportions and corresponding 95% confidence interval. The association of emesis control rate by gender and other socio-demographic and clinical covariates will be examined using Chi-square test, in case of small sample size Fisher's exact test will be used. Similar analysis will be performed to examine the secondary endpoints of complete control, complete emesis control and complete nausea control in the acute emesis period (the initial 24 hours after chemotherapy), delayed emesis period (the 24 - 120 hour period after chemotherapy) and in the control in the second cycle of chemotherapy.

Justification of sample size:
We anticipate to recruit a total of 50 patients for this study over one year after protocol approval, from prior experience with usage of carboplatin, we expect approximately 60% will be females. We project conservatively a 70% complete control rate based on prior literature (i.e. a 62% complete control rate in women and an 82% complete control rate in men). To evaluate the adequacy of the sample size (i.e. number of emesis control observed), we computed the precision, as measured by the width of the 95% CI, with which the proportion of emesis control rate can be estimated. The width of the 95% CI will be no greater than 26.7% (i.e. +/-the lower and upper limit of complete control rate will be 55.4% to 82.1%) with the proposed sample size based on exact Clopper-Pearson formula.

Review Bodies. The primary data monitoring and safety group will be the **Data and Safety Monitoring Board (DSMB).** This body will be constituted for this phase II trial. Information required in reports by this committee will include 1) summaries of accrual rates and patterns; 2) information on all adverse events and protocol violations; and 3) efficacy results at the time of each DSMB meeting, which will not be available to the investigators. Note, there is no interim

analysis specified for this trial. This committee will meet at least annually. The majority of the members will not be from any of the study institutions, and no member will be involved in any way with the study. Membership will include as a minimum: a statistician, a medical oncologist, and a research oncology nurse. Members of the DSMB are: Gregory Bizette, MD (Medical Oncologist, Ochsner Cancer Institute), James Symanowski, PhD (Biostatistician, Levine Cancer Institute), Patricia J. Hollen, RN, PhD, FAAN (Oncology Research Nurse; University of Virginia).

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