# Achieving control of CINV with $NK_1$ receptor antagonists: making the most of available medications

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My talk today is about $NK_1$ receptor antagonists and how to make the most of available medications.

## Disclosures

These are my disclosures.

## Pharmacological approach to CINV prevention

It is thought that chemotherapy induces nausea and vomiting by releasing certain neurotransmitters such as serotonin in the gut or dopamine and substance P in the central nervous system.

## Approved $NK_1$ RAs: CINV prevention

Therefore, a pharmacological approach to prevent chemotherapy-induced nausea and vomiting, or CINV, was to design antiemetics that would block these neurotransmitters, for example, dopamine D2 receptor, serotonin type 3 receptor, and $NK_1$ receptor for substance P.

## MASCC/ESMO 2016 antiemetic guidelines summary: acute CINV prevention

One recent advance was the development of NEPA, shown here in blue. NEPA is the first combined antiemetic where netupitant and palonosetron are combined, and unlike the other antiemetics that block only one receptor type, NEPA blocks two receptor types at once.

These are currently approved $NK_1$ inhibitors — aprepitant and its i.v. prodrug, fosaprepitant, rolapitant and netupitant, which is never used alone, but always with palonosetron in a fixed combination in NEPA.

$NK_1$ inhibitors are recommended for CINV prevention in combination with other antiemetics for single-day chemotherapy. Aprepitant is also recommended for multiple-day cisplatin and high-dose chemotherapy, and these medications should never be used for rescue treatment or for established nausea and vomiting.

Here you can see MASCC/ESMO guidelines for the prevention of acute CINV after single-day chemotherapy, and $NK_1$ inhibitors are recommended for high emetogenic chemotherapy, either non-AC, for example, cisplatin-based, or AC containing anthracycline and cyclophosphamide combination for patients with breast cancer, as well as for carboplatin.

The indication for carboplatin represents the latest expanded indication for these medications, after it was observed that carboplatin is the most emetogenic agent in the moderately emetogenic group

**Benefit of adding $NK_1$ RAs with carboplatin: complete response (no vomiting and no rescue)**

This year, a meta-analysis was published that further supports the benefit of adding an $NK_1$ inhibitor into the regimen for the prevention of nausea and vomiting after carboplatin, and here you can see the results for complete response.

The addition of $NK_1$ inhibitor, in blue, resulted in significantly better complete response rate, especially in the delayed and overall period where the difference was more than 10%, which is also considered by MASCC as clinically relevant.

**Benefit of adding $NK_1$ RAs with carboplatin: complete response: no nausea**

The same result was achieved for no nausea. The difference, especially in delayed and overall periods is, again, more than 10%, which is clinically meaningful.

**NEPA and APR/PALO in carboplatin subset: overall complete response**

The meta-analysis that I have just shown didn't include NEPA, so I would like to present here the results of NEPA and aprepitant/palonosetron in the carboplatin subset of patients from the one of phase 3 NEPA trials.

The regimen based on NEPA in blue and that based on aprepitant/palonosetron in grey are presented together on this slide, although the comparison was not formal.

You can see that NEPA achieved very high overall complete response rates, from 80% in the cycle 1, up to more than 90% in subsequent cycles.

**NEPA and APR/PALO in carboplatin subset: overall no significant nausea**

A similar result was achieved for nausea. Overall no significant nausea rate was 84% in the cycle 1, and up to 96% in the cycle 4. This is the only trial that evaluated the efficacy of $NK_1$ inhibitor in multiple cycles of carboplatin.

Based on these results, NEPA is also recommended for carboplatin.

**The benefit of adding $NK_1$ RAs in the prevention of CINV: carboplatin vs oxaliplatin**

This is another meta-analysis that evaluated the benefit of adding $NK_1$ inhibitors in the prevention of CINV after carboplatin and oxaliplatin.

While the benefit is well documented for carboplatin, it is still being discussed for oxaliplatin, and this meta-analysis gave us the answer for all three categories of response—complete response, no emesis, no nausea. Absolute relative difference was more than 10% for carboplatin only.

As I said, this is clinically relevant, so today $NK_1$ inhibitors are recommended for carboplatin, but not for oxaliplatin.

**Question 1**

Having covered the guidelines for the use of $NK_1$ inhibitors, I would like to ask you what would be your main criterion when deciding which $NK_1$ inhibitor to use?

Efficacy—one is more effective than the other?

Safety—one is better tolerated than the other?

Pharmacology—for example, availability of different routes of administration, drug metabolism, potential for drug–drug interactions?

Finally, convenience of dosing schedule—how simple it is to implement it?

Please vote.

**$NK_1$ RAs: efficacy**

For those of you who have voted for efficacy, let me tell you that the guidelines consider all $NK_1$ inhibitors as interchangeable based on clinically relevant improvement in complete response for CINV prevention, so you may use any of them.

Vomiting is better controlled than nausea with these medications.

The review on data on chemotherapy-induced nausea prevention from pivotal $NK_1$ inhibitor trials revealed differences among $NK_1$ inhibitors, with NEPA showing the most promising profile.

Of course, these data were noncomparative until this year when the first direct phase 3 head-to-head comparison was published.

**NEPA vs APR/GRAN regimen: HEC cisplatin**

Here you can see the design of the study. This study compared the NEPA-based regimen with the aprepitant/granisetron regimen in chemotherapy-naïve patients scheduled to receive their first cycle of highly emetogenic cisplatin-based chemotherapy. This study was an international study conducted in Asia.

NEPA-based regimen was compared with aprepitant/granisetron-based regimen. Both were combined with oral dexamethasone. NEPA was given only once per cycle, on day 1 only, and aprepitant followed a standard 3-day regimen.

**NEPA vs APR/GRAN in HEC cisplatin: complete response**

These are the results. The aim of the study was to document noninferiority of NEPA, and as you can see, by complete response, NEPA was noninferior. In the overall period, 74% of patients treated with NEPA were completely prevented compared with 72% of patients receiving aprepitant/granisetron.

**NEPA vs APR/GRAN in HEC cisplatin: no significant nausea**

The same result was achieved for no significant nausea. Therefore, noninferiority was demonstrated also for nausea. In the overall period, 76% of patients treated with NEPA were without no significant nausea, compared with 70% of patients in the aprepitant/granisetron arm.

**NEPA vs APR/GRAN in HEC cisplatin: QoL, the impact of CINV on daily living**

Another way to look at the efficacy is to evaluate quality of life and the impact of nausea, vomiting, or both on patients' daily living. Here you can see it for both NEPA in blue and aprepitant/granisetron in grey in the acute and delayed phases.

In the acute phase, there was no difference between the two treatment arms. A similar percentage of patients reported no impact due to nausea, vomiting, or both.

However, in the delayed phase, there was statistically significant difference in the nausea domain. 71% of patients treated with NEPA reported no impact on daily living due to nausea compared with 65% of patients receiving aprepitant and granisetron.

To me, this slide also nicely illustrates how vomiting is generally better controlled than nausea with $NK_1$ inhibitors.

A higher percentage of patients reported no impact on daily living due to vomiting compared with nausea in the delayed phase for NEPA, and the same pattern was also shown for aprepitant/granisetron.

Therefore, efficacy is not of much help when deciding which $NK_1$ inhibitor to use.

**Safety of $NK_1$ RAs: oral formulations**

For those of you who have voted for safety, let me say here that, generally, the toxicity profile of oral formulations of $NK_1$ inhibitors is low. These medications improved CINV prevention without significant safety concerns, including cardiac safety concerns.

In the first head-to-head comparison study that I have just shown, NEPA and aprepitant/granisetron showed similar incidence of adverse events.

Most common treatment-related adverse events were constipation and hiccups of low frequency and of mild-to-moderate intensity.

In the nonformal comparison of NEPA and aprepitant/PALO, again, a similar incidence and type of adverse events were observed in single and multiple treatment cycles, and the most frequent NEPA-related adverse events were constipation and headache.

**$NK_1$ RAs: safety of i.v. formulations**

On the other hand, safety may be an issue with i.v. formulations of $NK_1$ inhibitors.

This year, the distribution of rolapitant, of i.v. formulation of rolapitant was suspended in the US due to anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions.

The risk of serious hypersensitivity reactions is also reported in the product information for i.v. fosaprepitant.

In the clinical development programme for i.v. NEPA, a similar safety profile to oral NEPA was observed—no infusion-site reactions—and although there is a potential risk of hypersensitivity reactions due to palonosetron component, these reactions so far haven't occurred.

**Question 2**

This brings me to my second question: When selecting among the antiemetic regimens of similar efficacy and safety, what would be your main criterion—cost, pharmacology, or convenience of dosing schedule?

Please vote.

More than half of you voted for cost, and then almost half for convenience of dosing schedule.

Let's pretend that we live in an ideal world where cost is not an issue, and let's focus on the two other criteria, that is, pharmacology and convenience of dosing regimen.

**$NK_1$ RAs: pharmacology**

All $NK_1$ inhibitors are highly selective for $NK_1$ receptors and have a high affinity for these receptors.

All of them are metabolised through CYP3A4, aprepitant more extensively. Therefore, aprepitant has a much shorter half-life than the other two and has to be given in a 3-day regimen, while netupitant and rolapitant are given once per chemotherapy cycle.

As I said before, aprepitant and netupitant both have oral and i.v. formulation, netupitant in i.v. NEPA, and distribution of i.v. formulation of rolapitant has been recently suspended.

**$NK_1$ RAs: drug–drug interactions**

Drug–drug interaction—this is an important aspect of pharmacology. Both aprepitant and netupitant are metabolised through CYP3A4, aprepitant more extensively.

Both of them are also inhibitors of CYP3A4. This may lead to the increased exposure to medications which are metabolised through CYP3A4 if they are coadministered with aprepitant and netupitant. That is why you should reduce the dose of dexamethasone and monitor for adverse events with midazolam and some chemotherapy agents metabolised by CYP3A4.

This interaction with chemotherapy agents so far is considered nonsignificant because although there is an increased exposure, the incidence of adverse events is not higher, so there is no need to adjust the dose of chemotherapy.

The drug–drug interaction profile of aprepitant is more significant than that of netupitant. Rolapitant, on the other hand, although it is metabolised through CYP3A4, is not an inhibitor or inducer, so there is no need to reduce the dose of the dexamethasone.

Rolapitant is an inhibitor of CYP2D6, and CYP2D6 participates in the metabolism of all setrons except granisetron, which may limit the choice of setron partner for rolapitant.

In the new version of NCCN guidelines, it is stated that rolapitant has fewer DDIs compared with the other two.

**Convenience of dosing schedule: MASCC/ESMO HEC cisplatin**

Let me close with the last criterion, and this is the convenience of dosing schedule. Here you can see MASCC/ESMO guidelines for highly emetogenic cisplatin-based chemotherapy.

In the acute phase a 3-drug regimen is recommended, with $NK_1$ inhibitor in blue, setron in orange, and dexamethasone in green.

If you use aprepitant on day 1, it should be continued also on days 2 and 3. Metoclopramide has shown a similar efficacy in the delayed phase, so you may use metoclopramide instead.

If you use other $NK_1$ inhibitors they are given on day 1 only, and, of course, dexamethasone should be continued in the delayed phase.

**$NK_1$ RAs: convenience of dosing schedule HEC cisplatin**

This slide shows the number of antiemetic administrations. Every administration of an antiemetic is calculated as one, regardless of the number of pills, and you can see it for different antiemetic regimens containing different $NK_1$ inhibitors.

On day 1, this number is always three, except for NEPA, because in NEPA $NK_1$ inhibitor and setron are already combined.

**Convenience of dosing schedule: MASCC/ESMO HEC cisplatin**

Unlike the others, aprepitant has to be continued on day 2 and day 3, so together with dexamethasone, NEPA has the lowest number of antiemetic administrations.

**Convenience of dosing schedule: MASCC/ESMO HEC-AC (breast cancer)**

This is the recommendation for AC in breast cancer. Again, a 3-drug regimen should be used for the prevention of acute CINV. If aprepitant is used on day 1 it should be continued also on days 2 and 3.

Dexamethasone has shown similar efficacy in the delayed phase, so you may use dexamethasone instead.

For other $NK_1$ inhibitors, there is no need to use anything for prophylaxis or for delayed emesis and, again, NEPA has the lowest number of antiemetic administrations.

**Convenience of dosing schedule: MASCC/ESMO MEC-carboplatin**

Now for carboplatin. These are the recommendations for carboplatin, the new expanded indication for $NK_1$ inhibitors. Again, a 3-drug regimen in the acute phase.

Aprepitant should be continued in the delayed phase with other $NK_1$ inhibitors. No need for anything else for the delayed prophylaxis, and, again, NEPA has the lowest number of antiemetic administrations, and it seems that NEPA has the most convenient dosing schedule for physicians to implement and patients to follow.

**Question 3**

Unfortunately, not all of us have $NK_1$ inhibitors available, especially for AC chemotherapy and carboplatin. Therefore, my last question is if $NK_1$ inhibitors are not available in your country, which antiemetic would you choose as an alternative: thalidomide, olanzapine, or ginger? Please vote.

**Conclusion: $NK_1$ RAs**

Let's conclude. Guidelines consider all $NK_1$ inhibitors equally effective for CINV prevention.

No differences in efficacy and tolerability were identified between NEPA and aprepitant/granisetron regimens in the first comparative study published this year.

The choice of $NK_1$ inhibitor may be influenced by convenience of antiemetic schedule, availability of different routes of administration, drug–drug interactions and cost.

Thank you for your attention [*applause*].

[*Ends*]