Prophylaxis and Management of Chemotherapy-Induced Nausea and Vomiting: A Comparison of How the Experts Practice

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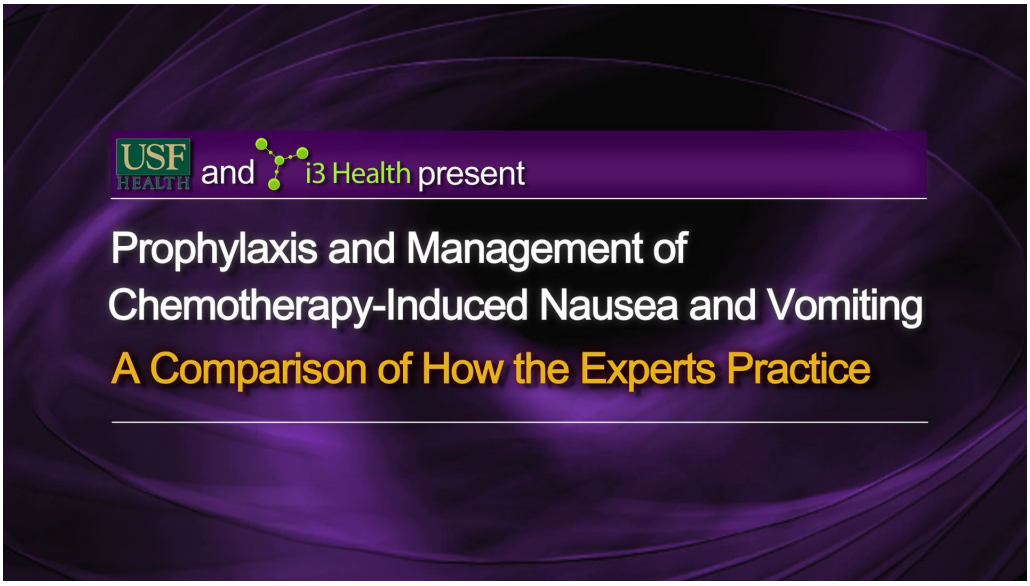
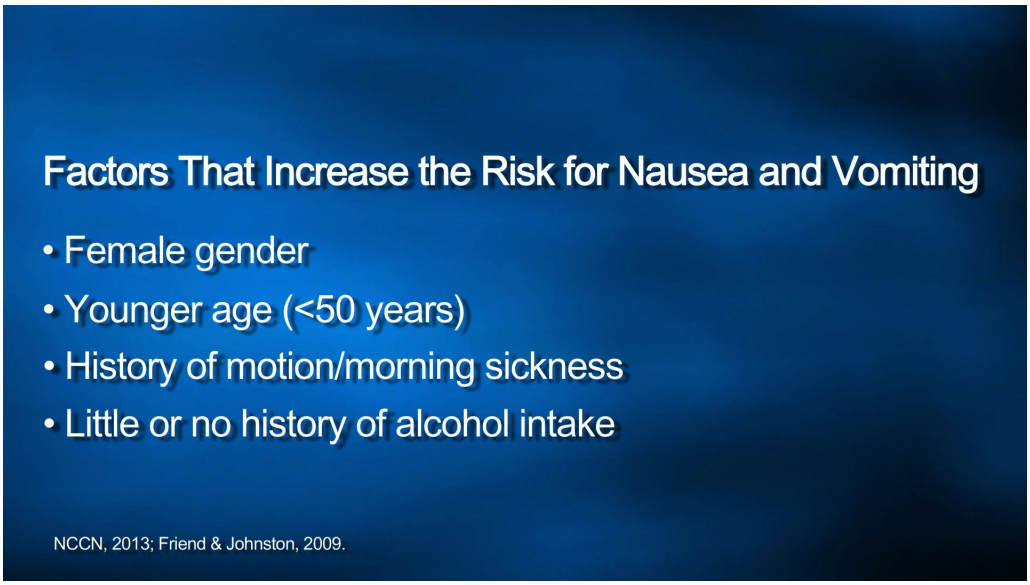


I. CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING: SCOPE OF THE PROBLEM

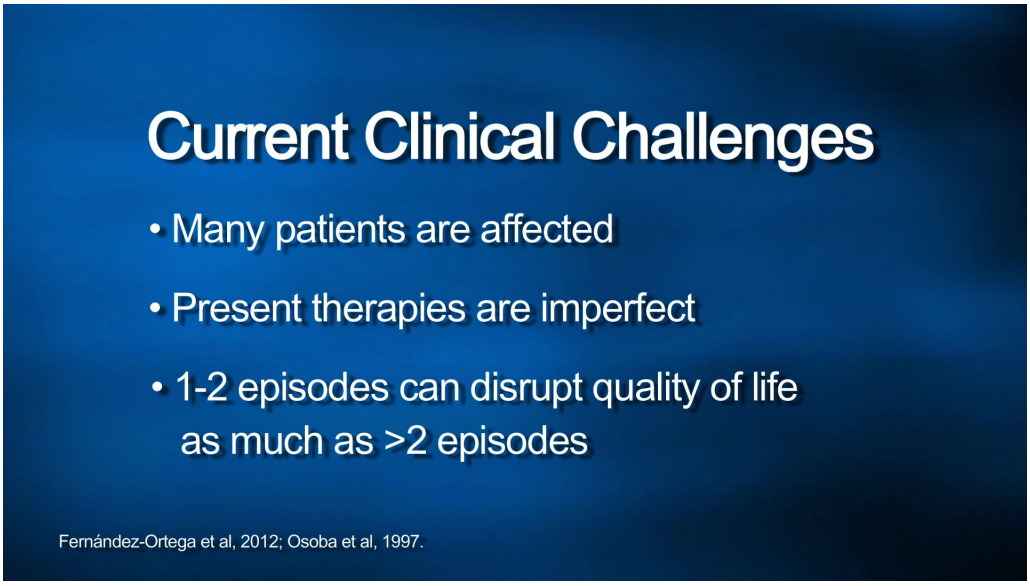
Mark G. Kris, MD: When patients face cancer therapy and visit an oncologist, the first questions they ask are: *What are the side effects of this treatment? Do these side effects include nausea and vomiting? What can be done about these side effects?* These questions are asked despite the fact that many of our cancer drugs do not have nausea and vomiting as a serious side effect and we have effective treatments for nausea and vomiting that have been developed over decades now. These treatments are available in every hospital and pharmacy in the world. These treatments are readily available to every patient. Physicians know how to use them. They're safe. Yet we still have a problem today. Why is that?

David S. Ettinger, MD: I think patients have this fear because we tell them chemotherapy has side effects, including nausea and vomiting, and some regimens are associated with a significant amount of nausea and vomiting. The other problem is some patients have a preconceived notion of nausea and vomiting. Usually they tell you they had a friend who had cancer and experienced significant nausea and vomiting—sometimes 20 years ago when the antiemetics weren't that good. Then you have to discuss with them the kind of cancer their friend had, it's not the same as theirs, and the chemotherapeutic agents were different and the antiemetics were different. What makes it difficult for them is they equate chemotherapy of any type with nausea and vomiting. The patients who usually talk to you about this are women, particularly younger women. Obviously, you have to talk to them about what other things can cause nausea and vomiting. A history of motion sickness

increases their risk, which I think is important. Have they experienced nausea and vomiting with nonchemotherapeutic agents? Usually I tell a patient if you say you're going to be sick, you're going to be sick. You have to have a different mindset.



Steven M. Grunberg, MD: Of all the side effects that we deal with, you might say it's one of the best known and most familiar to our patients. We can tell a patient that you're going to have numbness and tingling in your fingers and toes. Perhaps our patients with diabetes will understand what that means but otherwise it's an unusual concept. Nausea and vomiting is something that everybody understands. Beyond that our present remedies are not perfect. Even if we've been able to decrease the amount of nausea and vomiting by 90% that's sort of like saying you treated a cancer and you killed 90% of it. That doesn't mean it completely went away. Quality-of-life studies have shown that one or two vomiting episodes can be as damaging to a person's quality of life as a larger number of vomiting episodes, so the bad press—perhaps the justified bad press—of nausea and vomiting still exists.



Dr. Kris: Knowing that patients are going to have this concern what recommendations would you make to other physicians or nurses dealing with this problem?

Dr. Grunberg: We try to be honest with our patients and tell them what to expect. We don't try to hide the fact that nausea and vomiting is a risk. We try to emphasize that it is one that we've become much better at addressing and that we have many different weapons with which to fight it. We are going to give them the best first-line regimen that we can but if that should not work we need to know about it right away because there are other things we can do. We also try to talk to them about things that they can do. We emphasize to our patients that staying hydrated is perhaps the most important thing they can do during the time of chemotherapy. Even if you do not feel that you can eat a full meal, maintain your hydration. It gives them something that they can focus on to help themselves. If our patients feel that they can help themselves that often helps them develop a more positive attitude and get through the experience.

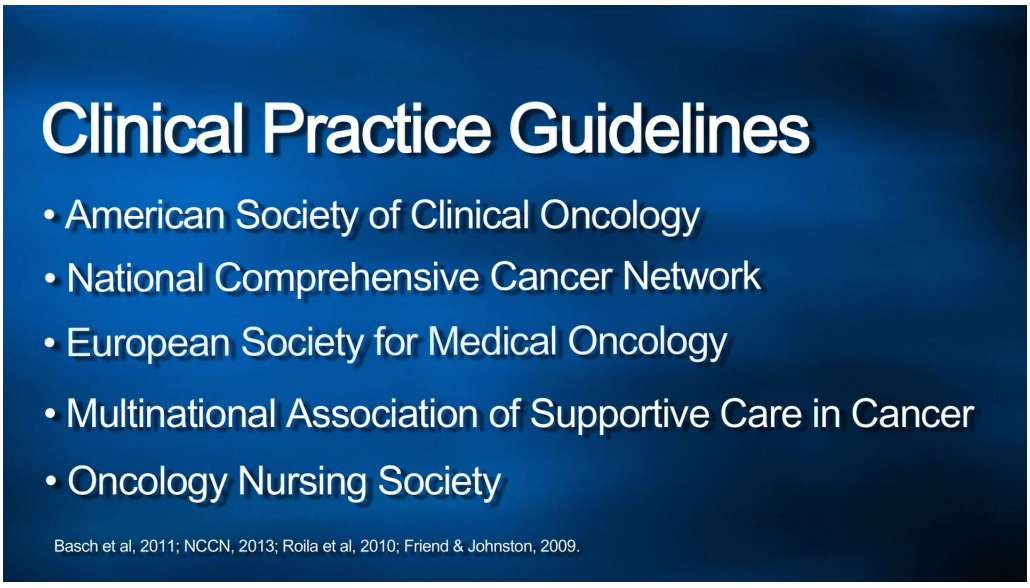
Dr. Ettinger: We have ancillary medicines that can help them overcome some of these side effects. For example, lorazepam might be helpful if they have anxiety. The ultimate goal really is to tell them that we're trying to prevent the nausea and vomiting and we have appropriate medicines that allow us to do that.

Dr. Kris: I think that prevention message is key. It's very important to state that everybody caring for the patient is committed to preventing nausea and vomiting: the oncology nurse giving the chemotherapy, the nurse teaching the patient, the physician. We're all committed to doing it. We're going to be proactive about it.

II. APPLYING ANTIEMESIS GUIDELINES IN PRACTICE

Dr. Kris: The guidelines have been a critical means of standardizing the care of patients and ensuring that the best regimens that have been tested in clinical trials where there's the best evidence are actually given to patients. Are there differences within guidelines among the different guideline organizations?

Dr. Ettinger: In my opinion, actually, the guidelines from the American Society of Clinical Oncology, the National Comprehensive Cancer Network, the European Society for Medical Oncology, the Multinational Association of Supportive Care in Cancer, and the Oncology Nursing Society are very similar. Where guidelines change is when they get to the individual health system or individual institution.



Dr. Grunberg: In terms of adherence to guidelines, it's very good when there's a high adherence to guidelines because that means the best general principals are being followed most of the time, which is probably as it should be. If I hear about 100% adherence to the

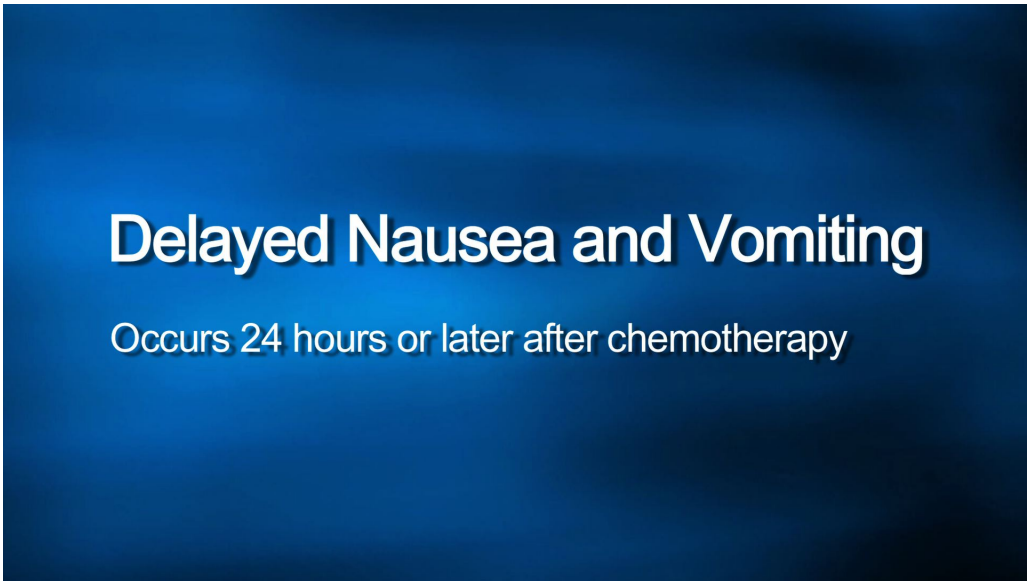
guidelines, I get worried because that means you've stopped thinking about your patients and stopped thinking about the individual differences that might come up in certain cases.

Dr. Kris: The number that I've thrown out is 80%. I think a good benchmark would be that 80% of the time decisions for the patient should be in accordance with the guidelines.

When you think about preventing emesis—the number one concern of virtually every person receiving cancer therapy—that is a huge goal. People have to be reminded of what our patients are asking us, what they deserve, and what we can do. The truth is we can deliver. Also, yes, there's cost but what are you getting for the cost? I don't think anybody's going to say that what we're getting for the cost of these antiemetics is not worth it.

III. CASE I: DELAYED NAUSEA AND VOMITING

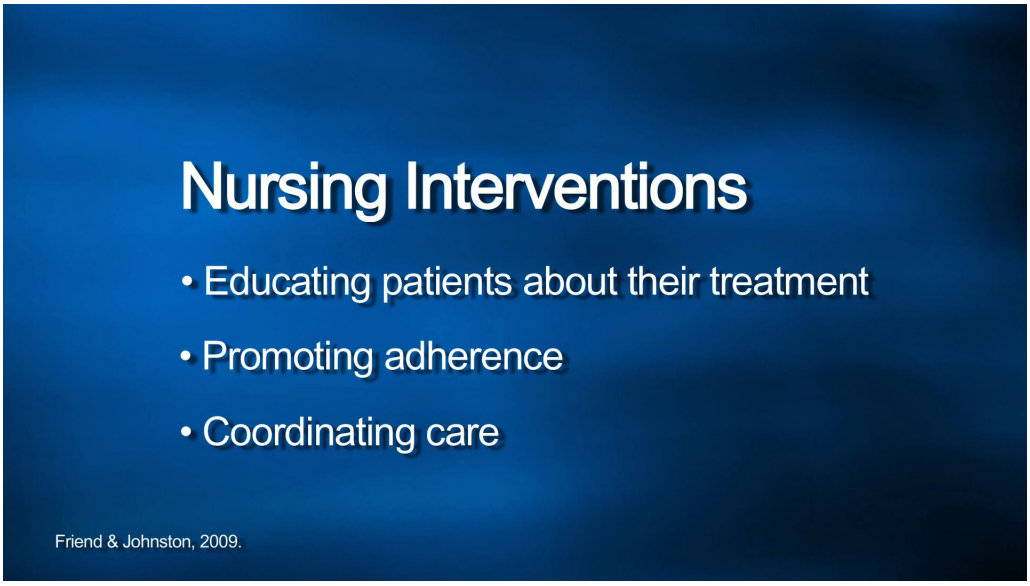
Dr. Kris: We are going to discuss three patients today, each of them being used as a springboard to talk about different aspects of preventing and treating nausea and vomiting in persons with cancer. The first case focuses on so-called delayed emesis. Delayed emesis is actually any nausea and vomiting that occurs anytime along the spectrum of care. Arbitrarily it's defined as occurring 24 hours or later after chemotherapy but if it's 19 I think that's delayed as well. And it can go out for 5 days.



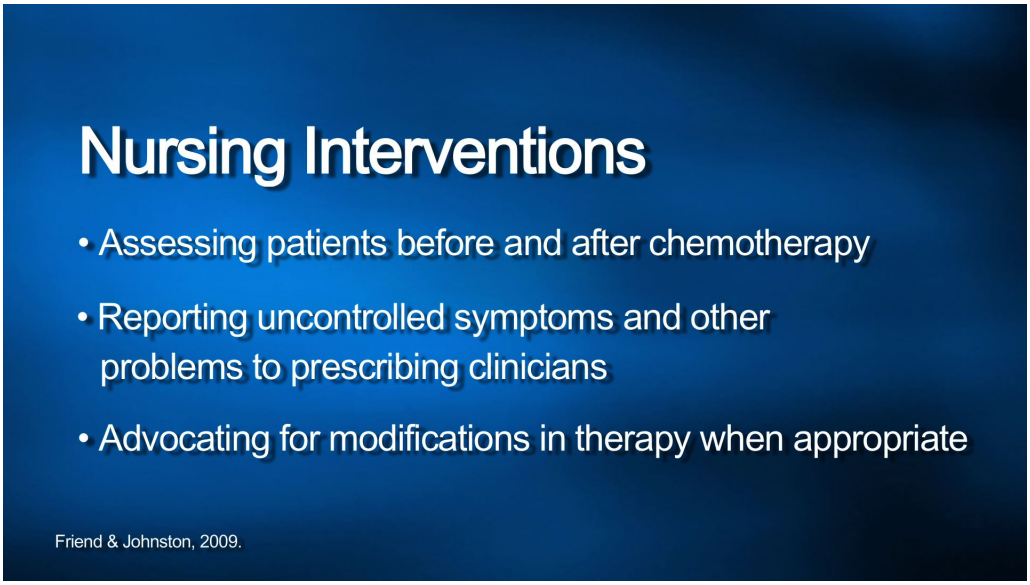
Ms. JW is a woman with node-positive, triple-negative breast cancer who underwent lumpectomy. I recommended a combination of cyclophosphamide and doxorubicin to be followed by paclitaxel. We talked about the various side effects and what to expect. The very first thing that Ms. JW said was that she was very concerned about nausea and emesis. She was afraid that it would interfere with her ability to do her job. She was an accountant and there was a tax deadline virtually all the time. She had clients that she had cared for year in and year out and she just didn't want to let them down. Letting those people down would have been an additional burden on her on top of everything she was facing with cancer.

The first thing I tried to do in this situation was to address Ms. JW's concerns and explain as clearly as I could that we share her concerns and we have effective treatments that can prevent vomiting in the vast majority of patients and lessen or prevent nausea in a large number of patients. Everything that we could do would be done to prevent her symptoms.

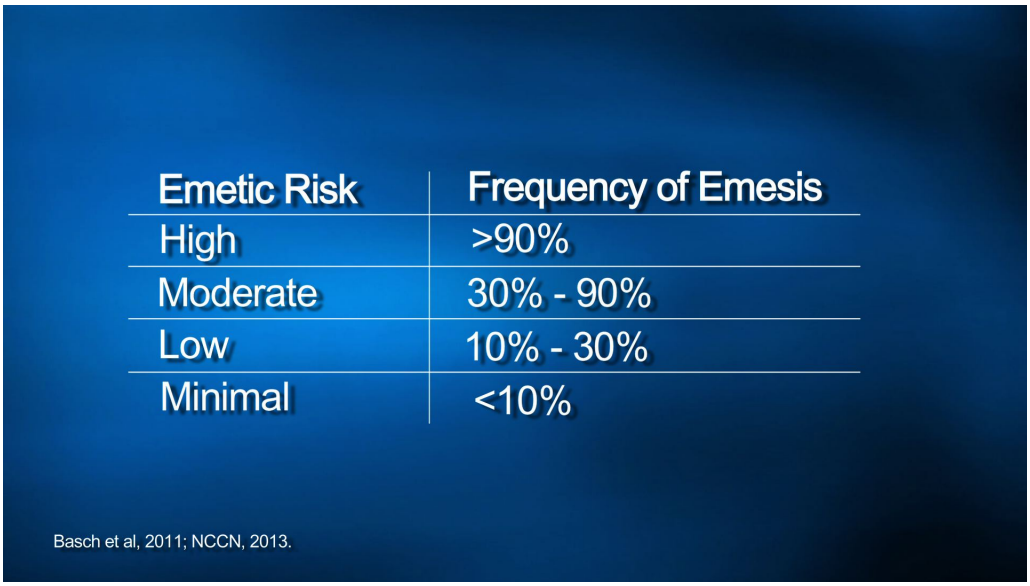
Also, I let her know how single minded we all are about this. I'm part of the team but I also work closely with an oncology nurse who is available to ensure that the treatments that are prescribed are acquired and given and that all questions about how to take the medicines are answered, to help the patient understand the need to take these medications over several days because the problem lasts for several days, and to coordinate with the other physicians and nurses involved in the cancer treatment—the people that actually give the chemotherapy and any others that may be stepping in for some aspect of the care.



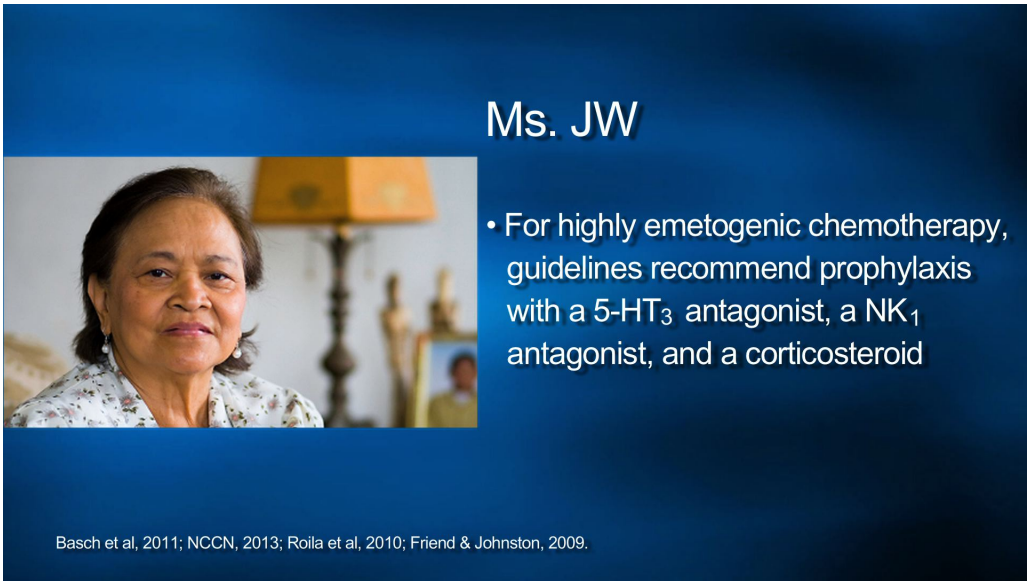
I think it's important to acknowledge the problem, address what's being done about it, allow a chance for education, and make sure we have clear communication about where things stand. If patients have questions or things are not going right we need to know because problems can be dealt with quickly and effectively. We have to make this a standard part of our discussion. It goes not just for the antiemetics but also for every aspect of cancer care.



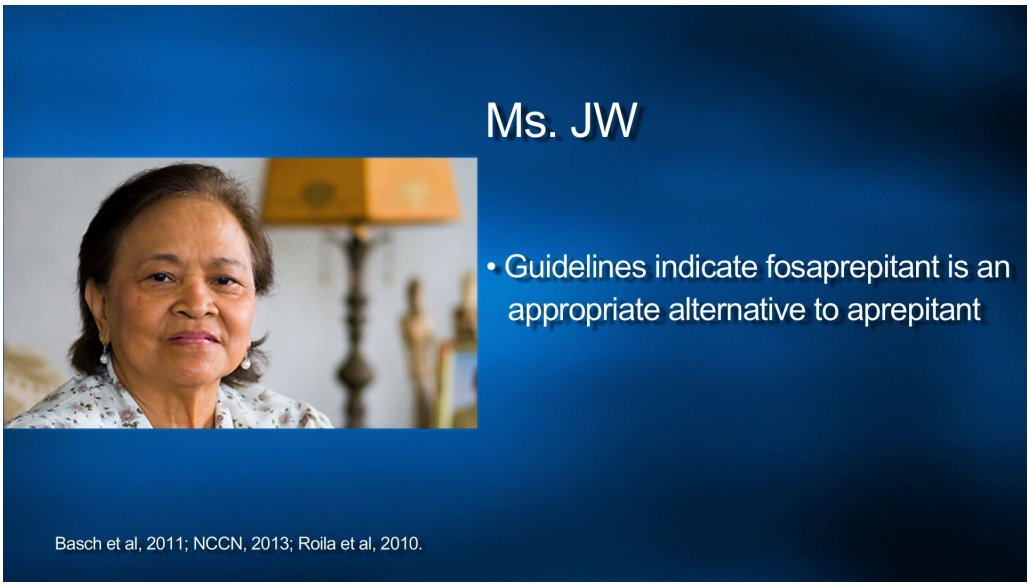
The combination of an anthracycline, in this case doxorubicin, and cyclophosphamide is commonly used in breast cancer treatment and what most guidelines consider highly emetogenic. The amount of nausea and emesis that you can expect from this regimen, even though historically it has been classified as moderate in some settings, is indeed high. By high we mean a more than 90% chance of having vomiting during the treatment period. When does that vomiting occur? Nowadays the vomiting occurs most likely in the so-called delayed phase, the time after 24 hours following the chemotherapy.



How much emesis do you see even with our best prophylaxis? At Memorial Sloan-Kettering, the quality assurance department evaluated outcomes after our antiemesis guidelines were used. The data showed that despite giving our best treatments, vomiting still occurred in 23% of women and nausea occurred in 59%. So I think this is a case that shows how well we've done but frankly how far we have to go. My institution would recommend a combination of the 5-HT_3 antagonist palonosetron, the NK_1 antagonist aprepitant, and dexamethasone for highly emetogenic therapy.



Dr. Ettinger: I would have done exactly what you would do. I would have used an NK_1 antagonist, I would have used palonosetron, and I would have used steroids. And as a matter of fact, rather than aprepitant, I would have used fosaprepitant.



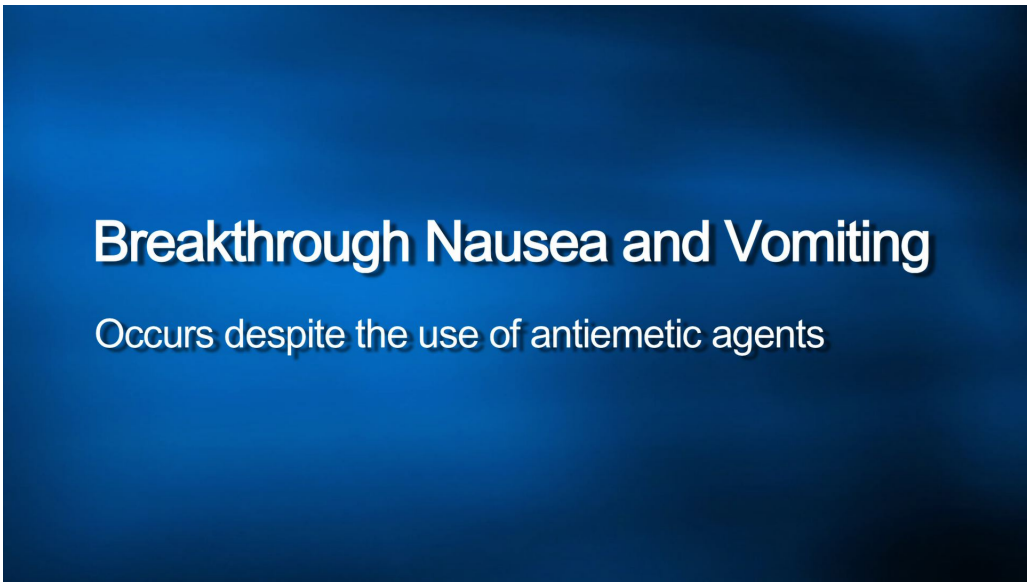
Dr. Grunberg: We tend to use fosaprepitant also because you can use it as a single dose rather than the multiple doses with your oral agent. It's easier. We administer it at the hospital. We don't have to worry about adherence. The overall cost to the health care

system as a whole is not that much different. With the intravenous fosaprepitant, there may be venous irritation. That's really the only difference.

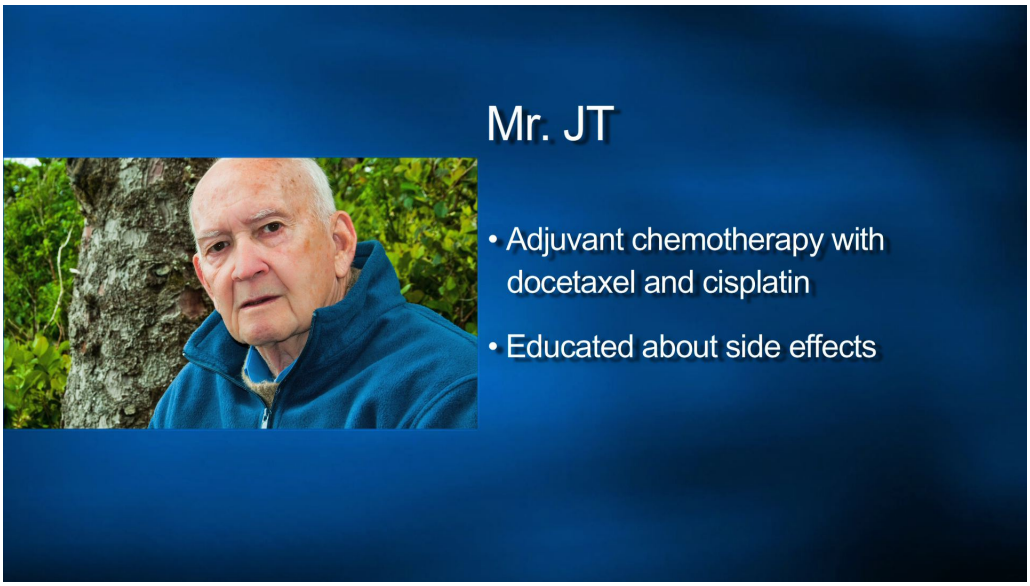
Dr. Kris: In summary, I think there is consensus that the combination of an anthracycline and cyclophosphamide causes a very high degree of nausea and emesis. Frankly, the degree of nausea and emesis, even with our best therapy, I would say is still unacceptable and it is a charge to all of us that we have to find a better way to help our patients. The combination of a 5-HT_3 antagonist, aprepitant, and dexamethasone is the optimal regimen for this patient. There's good evidence that the second-generation 5-HT_3 antagonist palonosetron is more effective than first-generation 5-HT_3 antagonists, particularly in terms of nausea, which is the number one problem our patients face. The available antiemetics are safe. And aprepitant clearly adds to the degree of control, particularly to vomiting less so for nausea.

IV. CASE 2: BREAKTHROUGH NAUSEA AND VOMITING

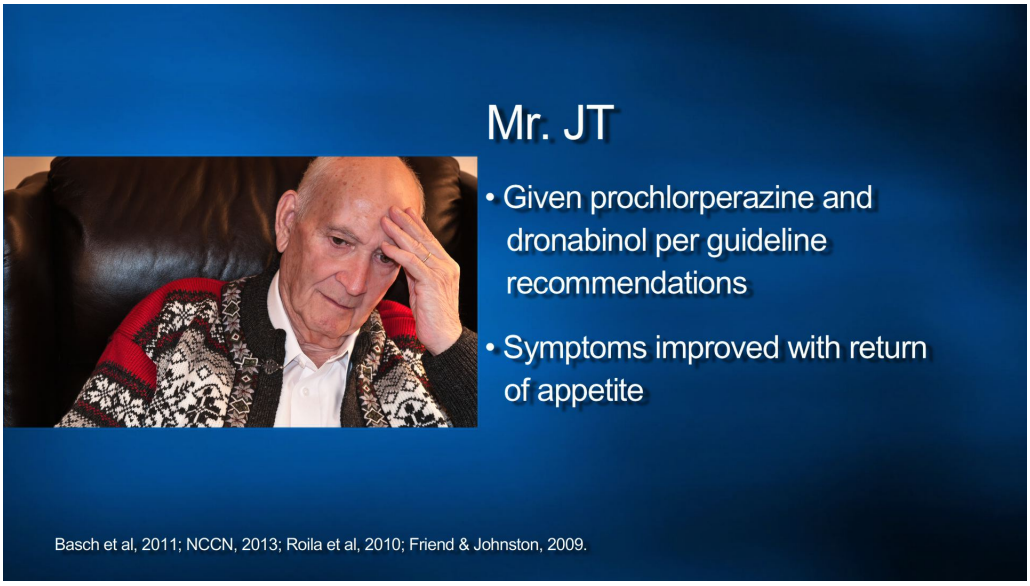
Dr. Kris: The second case we're going to discuss today deals with the problem of breakthrough nausea and vomiting. That is a situation where despite giving the best available medicines to prevent nausea and emesis some nausea or emesis still occurs.



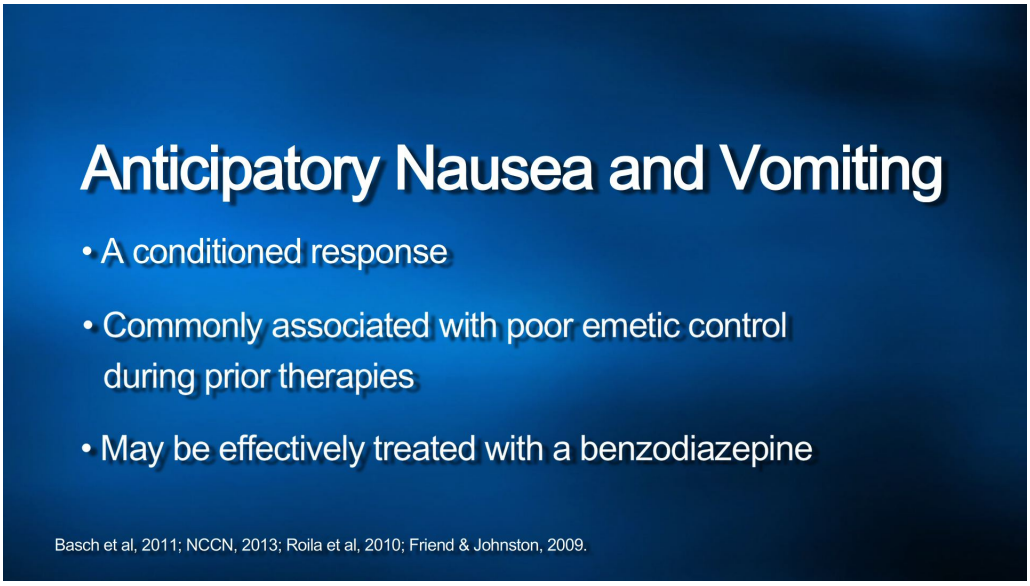
Dr. Ettinger: Mr. JT was a 70-year-old gentleman with stage II adenocarcinoma of the lung status postresection who came to me for adjuvant chemotherapy. I recommended that he receive docetaxel and cisplatin. I talked to him about the side effects associated with that regimen and he understood that the regimen was highly emetogenic. He was concerned about nausea and vomiting since he had experienced nausea and vomiting with other noncancer medicines he was taking. I gave him fosaprepitant, palonosetron, and dexamethasone.



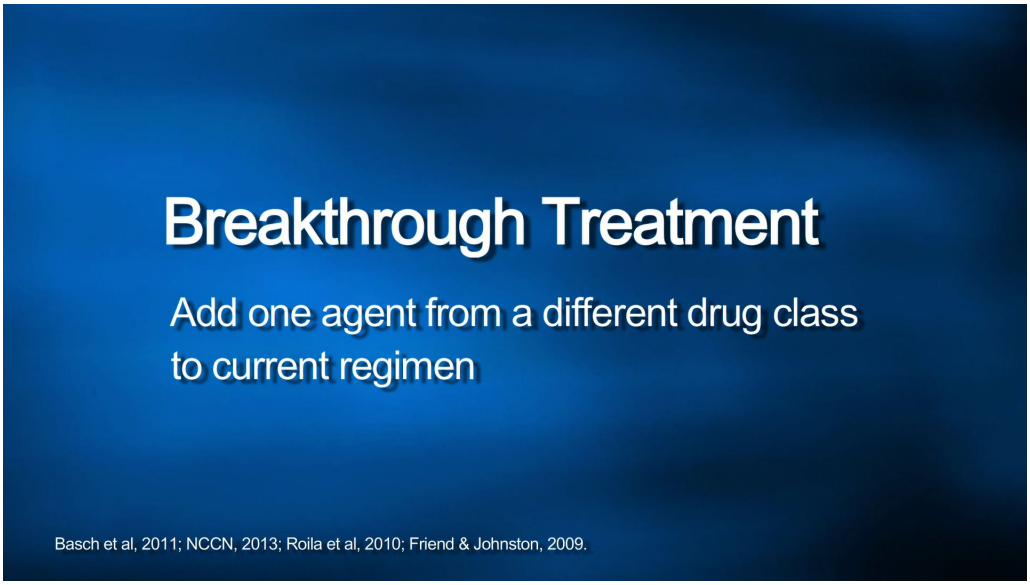
Twenty-four hours after Mr. JT started chemotherapy he experienced some nausea and vomiting, which persisted for 96 hours. However, at 48 hours he called the oncology nurse about his symptoms. The patient had already been given prochlorperazine to take if he had additional nausea and vomiting. We also gave him dronabinol. The patient actually did respond, with an improvement in his appetite. I would say he had a good reaction to the dronabinol.



Dr. Grunberg: This case has a lot of different possibilities. You're saying the patient developed nausea and vomiting 24 hours after the chemotherapy. He did receive a three-drug prophylactic regimen but you also pointed out the patient was quite anxious and had previous bad experiences. This is a patient who even without the first experience is already set up to have an anticipatory or learned response. So one thing we might try with this patient is an antianxiety agent. This might be the case where a benzodiazepine would indeed make a difference.



When we're looking at these patients, though, we also have to question them as to exactly what was happening and when it happened. Did the patient have a problem with vomiting? Did the patient have a problem with nausea? If it's a problem with vomiting, then you do ask yourself, well we've used three different families of antiemetic agents, are there any families we haven't used yet that might be effective? The D_2 antagonists actually may have a role in this area and a D_2 antagonist is not an unreasonable agent to add. What your favorite is can vary. We tend to use metoclopramide probably because one of our earliest trials was a straight out metoclopramide versus haloperidol trial—almost 30 years ago—where metoclopramide happened to do better for our patients. I don't think which D_2 antagonists you use is the key point. The key point is the antiemetics have different mechanisms. If the mechanisms that you're attacking haven't been sufficient try a new mechanism.



If the problem is more a nausea problem than a vomiting problem, you start looking at other agents. Sometimes merely extending the course of steroids will be enough to take care of a nausea problem. We also use cannabinoids specifically for nausea. I think that if there's a role for olanzapine, it's probably going to be more against nausea than it is against vomiting. With the antinausea drugs, you can often get the antinausea effects at a very low dose. Problems start occurring when the doses are escalated very high trying to turn them into antivomiting drugs.

Dr. Kris: I think I've been a so-called early adopter of olanzapine as part of a prophylactic regimen. There is a phase II trial indicating that this can be done. The data are pretty compelling that the agent does improve both nausea and vomiting, particularly nausea. I have been using it. I've had no safety issues. Patients report they've had the best sleep in a long time. That's particularly important in these situations because patients often have sleeplessness brought on by the dexamethasone. Dr. Grunberg's point about the benzodiazepine particularly where a patient may be anxious is important. You know when they do anxiety testing in any population of people facing initial chemotherapy anxiety scores often warrant treatment with a benzodiazepine or another antianxiety agent.

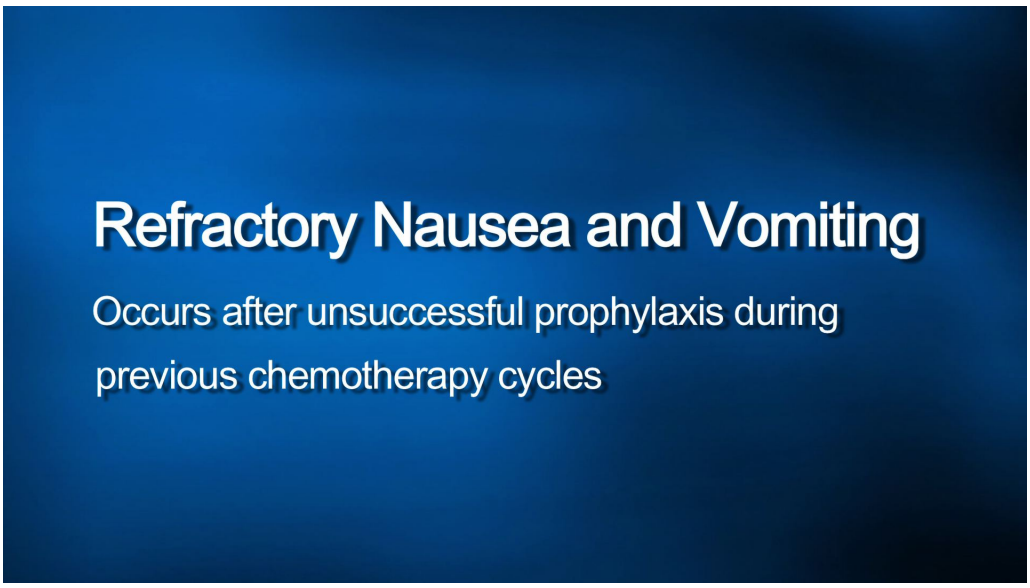
If I could draw some consensus here, breakthrough nausea and vomiting is a problem and as you work with patients initially you have to prepare them for it. Giving a prescription before chemotherapy is something that I think many of us do. Exactly what drug to give varies by practice. Dr. Ettinger would give prochlorperazine. Dr. Grunberg would in this case give a benzodiazepine. I would probably have given olanzapine. And also when the problem does happen consider switching to a drug from a different class.

Dr. Ettinger: There are some anecdotal data about switching to a different serotonin antagonist. Have you had that experience?

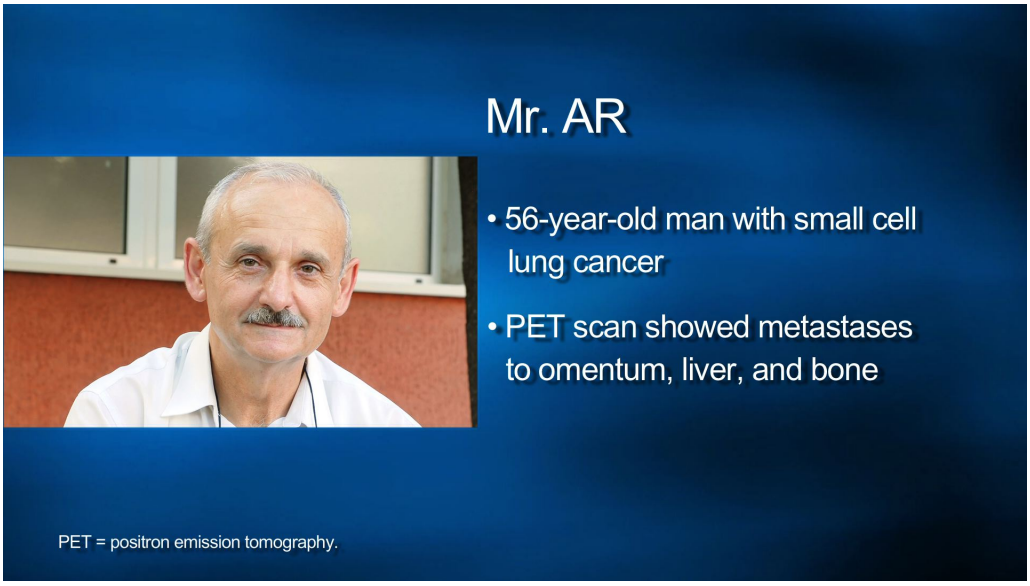
Dr. Grunberg: There's theoretical support that most of the first generation 5-HT_3 antagonists have basically the same mechanism of action but there may be some differences in the mechanism of action of palonosetron. There are some basic studies that have suggested more internalization of the 5-HT_3 receptor complex, for example, which might result in a more potent action. But these have really all been in laboratory trials. I do not know of a clinical trial that has actually been able to show this in a convincing way.

V. CASE 3: REFRACTORY NAUSEA AND VOMITING

Dr. Kris: The last case study focuses on refractory nausea and emesis. Refractory antiemesis is a term of art that refers to controlling nausea and emesis in a situation where a person has previously received antiemesis drugs and had nausea and vomiting despite receiving preventative drugs and other drugs during the course of their treatment. So the physician is now faced with the next cycle of chemotherapy. What do you do in the next cycle knowing that this patient had incomplete control during the first cycle?



Dr. Grunberg: Mr. AR was a 56-year-old man diagnosed with small cell lung cancer. Positron emission tomography scan staging revealed spread of disease to omentum, liver, and bone. He was started on etoposide and carboplatin. During the first cycle, he received a standard 1-mg dose of granisetron with a corticosteroid but still developed nausea and vomiting on the first night of chemotherapy. During the second cycle, he was rotated to a higher dose of a different 5-HT_3 antagonist, to ondansetron 16 mg, with dexamethasone but had even worse nausea and vomiting on the first night of chemotherapy. So the question is: Where do you go from there?



Dr. Ettinger: One of the first things you have to evaluate is other causes of nausea and vomiting. Mr. AR already has metastasis in his abdomen, mainly the liver. One of the other causes of nausea and vomiting is brain metastasis. One might consider getting a magnetic resonance imaging scan of the brain to look for other sites of metastasis. One would review the other medicines he's on as well to see if they can cause nausea and vomiting. Obviously, if you can rule out other causes then you're left with the classic case of refractory nausea and vomiting secondary to the chemotherapy. Then you would need different antiemetics with different mechanisms of action to try to alleviate his chemotherapy-induced nausea and vomiting. The other thing one could do is consider what part of this is anticipatory. There are other things we can do for anticipatory nausea and vomiting.

Dr. Grunberg: In this particular case, no other cause for the nausea and vomiting was found. The restaging did show that the patient was having an excellent response so he wanted to continue that particular chemotherapy. With the addition of an NK_1 antagonist and a benzodiazepine for the anxiety that had arisen from the first couple of cycles, the patient was able to get through further chemotherapy. Knowing that he was responding well also probably helped him move on.

Dr. Kris: I'd just like to echo your comment about looking for other causes of nausea and vomiting. It is important to consider other cancer-related causes and other medications—probably the biggest secondary cause. In a situation like this, I would probably go back to our standard high-dose regimen, which would be palonosetron, aprepitant, and dexamethasone. Dexamethasone given for multiple days for acute as well as delayed

episodes. Depending on how serious the problems were for this patient, this may be a case where I would immediately give olanzapine as well.

Dr. Ettinger: There's a third option. You may have to change the chemotherapy. I mean this is not with curative intent so obviously the goal is to give him the best quality of life for the longest period of time. Having nausea and vomiting is not good quality of life. You'll know after the second cycle of chemotherapy whether he's responding. The easy thing is if he's not responding you have to change the regimen anyway. If he is responding then you have to work around that in some fashion.

Dr. Grunberg: I think you addressed a lot of the points I was trying to bring out with this case. There is almost a reflex among physicians to say well if the nausea and vomiting isn't controlled we should just give more or bigger or better antiemetics without thinking about the other causes. In this patient with liver and omental involvement, there is also a reasonable chance of bowel involvement. You want to make sure the patient doesn't have a bowel obstruction before you give him a prokinetic agent. If there's omental involvement, if there's a lot of cirrhosal involvement, your patient may actually develop an ileus where you may actually need a prokinetic agent to help things along. You can also look for infection. You're going to look for electrolyte abnormalities. In small cell lung cancer, there are all sorts of different ones that one can see. I think all the strategies that were proposed are reasonable ones. One could rotate to the second-generation 5-HT_3 antagonists rather than merely rotating between first-generation 5-HT_3 antagonists or you can add on another family of agents. Or one might change the chemotherapy, or with certain regimens, one may even change the schedule and administration of the chemotherapy going to a longer administration, perhaps an infusion, to decrease the amount of emetogenicity.

Dr. Kris: In the case of a patient who had a poor result with prior treatment for nausea and vomiting despite our best efforts, it is important to look at all the possible causes of nausea and emesis—whether it be a concomitant medicine, an unexpected site of metastasis, or a paraneoplastic complication. Also important is looking at the antiemetics used and making sure the drugs were given and taken. Making sure the doses were correct. Thinking about alternative agents either in the same class or changing to a different class. Also raising a question about the chemotherapy, making sure that those drugs are benefiting the patient and switching to an alternative chemotherapy if that's possible as yet another strategy to manage a patient with refractory symptoms. ■

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