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## Investigating Plinabulin for Prevention of Chemotherapy-Induced Neutropenia

### Announcer Intro:

Welcome to ReachMD. The following program is a special edition of Project Oncology, sponsored by BeyondSpring Pharmaceuticals. BeyondSpring: bringing change to cancer care.

Here is your host, Dr. Matt Birnholz.

### Dr. Birnholz:

Severe neutropenia is one of the most dangerous potential complications of chemotherapy, exposing patients to high risks of infection which can ultimately prove fatal. In today's discussion, we'll explore the origins and impacts of severe neutropenia and focus on a novel research effort seeking to prevent this issue through a new pharmacotherapy.

This is ReachMD, and I am Dr. Matt Birnholz. My guest today is Dr. Douglas W. Blayney, oncologist and Professor of Medicine at the Cancer Institute of Stanford University School of Medicine. Dr. Blayney is a past President of the American Society of Clinical Oncology, or ASCO, and recipient of the inaugural Ellen Stovall Award for Leadership in Patient-Centered Care from the National Coalition for Cancer Survivorship. In his clinical research roles, he serves as principal investigator for a Phase II and Phase III trial investigating the role of vascular disrupting agent plinabulin for reducing the duration of severe neutropenia in cancer patients receiving myelosuppressive therapy.

Dr. Blayney, welcome to the program.

Dr. Blayney:  
Thank you.

### Dr. Birnholz:

So, Dr. Blayney, to start, let's get some more background on severe neutropenia. What can you tell us about the scope of this issue from your vantage point as an oncologist and cancer researcher?

### Dr. Blayney:

Well, severe neutropenia is a complication of myelosuppressive chemotherapy. Myelosuppressive chemotherapy we have used for 30 or 40 years now. It's a mainstay of treatment of a lot of solid tumors. We have used myelosuppressive chemotherapy for 30 or 40 years, as long as I've been practicing medical oncology. The target effect of chemotherapy is the cancer or the tumor—that's why we use it—but, if you will, an off-target effect is the bone marrow. Myelosuppressive chemotherapy, which we use and I don't think is going away soon, necessarily as part of its function produces a nadir, or a low white blood count, about day 8 or 10 after giving it, and the bone marrow normally recovers by day 21, and that's why we use chemotherapy every 3 weeks. The more chemotherapy or the more intense dose one gives, the deeper the myelosuppression. The longer the myelosuppression and the deeper puts patients at risk for febrile neutropenia.

We've come to understand in the past 30 years or so that there are certain chemotherapies that have a greater than 20% risk of febrile neutropenia, not just myelosuppression but febrile neutropenia, and it's those 20 or 30% of chemotherapy regimens which are still valuable in our treatment but are dangerous, as you put it, for the patient. So, dealing with the complications and preventing the complications of myelosuppression is one of the main goals we have in effectively using chemotherapy.

### Dr. Birnholz:

And on that note, Dr. Blayney, what are the current methods of managing or preventing severe neutropenia in practice, and what would

you say their limitations are at this point?

Dr. Blayney:

The one that most people are familiar with is use of a granulocyte colony-stimulating factor, or GCSF, filgrastim or pegfilgrastim. Our guidelines, both the ASCO and NCCN guidelines, suggest that that be reserved for primary prophylaxis or routine use to prevent febrile neutropenia for those chemotherapy regimens which have over 20% risk of febrile neutropenia. So, GCSF, filgrastim, pegfilgrastim, same thing, are the current ways we prevent complications of febrile neutropenia.

Another mechanism which is used sometimes is prophylactic antibiotics. That has a disadvantage, of course, of exposing people to antibiotics that don't need it, that won't benefit. Prophylactic antibiotics change the gut flora, can lead to complications of gut flora change including diarrhea and also spread antibiotic resistance.

One of the other ways to prevent febrile neutropenia is not use as high a dose chemotherapy. That is appropriate for many of the palliative settings where we use chemotherapy. For instance, when we use single-agent treatment for lung cancer, often reducing the dose one can get the same benefit, antitumor benefit, without exposing the patient to febrile neutropenia. So, dose reduction is a valid way, and by that I mean chemotherapy dose reduction is a valid way.

So, in summary, filgrastim or pegfilgrastim, second would be prophylactic antibiotics, and third would be dose reduction are our current treatments.

I should say that pegfilgrastim often causes a lot of bone pain. Pegfilgrastim has to be used the second day after chemotherapy, so that means patients have to come back into the office or the infusion suite on the second day. Lately, we've started using Onpro, which is a mechanical device which delivers the chemotherapy dose the day after the patient leaves the infusion suite. This is one of the ways we do it, but it doesn't mitigate the bone pain.

Dr. Birnholz:

I see. So, clearly, despite the options that are available, there are some significant limitations to these options, which I think brings up a good entrée into my next question for you, which is to really start to hone in on the drug molecule that you've been actively investigating in clinical trials, which is this vascular disrupting agent I mentioned earlier called plinabulin. How did you become interested in this molecule specifically and get involved in its research?

Dr. Blayney:

Well, thanks. That's an interesting question. Not much has happened in the mitigation or prevention of febrile neutropenia in the last 20 years since pegfilgrastim was approved. When plinabulin was tested in a bunch of lung cancer patients in combination with Taxotere, it was noticed that the patients who got plinabulin plus Taxotere not only had a slightly better or better tumor outcome but also had decrease in the amount of grade 3 and grade 4 febrile neutropenia, so this led to the question: Gee whiz, if it doesn't have as much grade 3 or 4 toxicity and may have some anticancer effects, shouldn't we be testing this plinabulin compound in the setting of myelosuppressive chemotherapy and trying to prevent febrile neutropenia, and maybe it doesn't have the same problems as some of the pegfilgrastim, filgrastim treatments?

Dr. Birnholz:

And I understand that there's a mechanistic difference here compared to other neutropenia-preventing drugs. Talk to us about that.

Dr. Blayney:

Yes, just as a reminder, filgrastim and its long-acting conjoiner pegfilgrastim do two things. One, they release mature neutrophils from stores, so you get a bump in the neutrophil count about day 2 or 3 after pegfilgrastim is given, and then, the nadir is narrower and you get a quicker recovery because pegfilgrastim accelerates the maturation of neutrophil precursors. What we understand, and it's really not well understood currently, is the mechanism of action of plinabulin. Plinabulin probably affects the dendritic cells in some way and may protect the neutrophil precursors and the mature neutrophils from damage by myelosuppressive chemotherapy, but, again, we're early in our understanding of mechanism of action of plinabulin.

Dr. Birnholz:

Now, Dr. Blayney, you alluded to this a little bit before, but talk to us again a little bit more specifically about how plinabulin differs from biologics for preventing neutropenia.

Dr. Blayney:

We don't understand exactly how plinabulin works, but, as a practical matter, it seems that it can be given on the same day of chemotherapy so patients only have to come to the office once or infusion center once. They don't have to return the next day or get some other mechanism, so plinabulin can be given on the same day as the chemotherapy. Furthermore, it looks as if plinabulin doesn't

have the bone pain side effect that pegfilgrastim and filgrastim does, so there may be a couple clinical advantages there from a point of view of the patient and the physician. Finally, it's hard to know because the drug, first, hasn't been approved or what the price will be, but one of the problems with filgrastim and pegfilgrastim is the expense. It looks like plinabulin, which is a complex but is a small molecule, can be synthesized and may not have the expense of pegfilgrastim. That's, again, a speculation on my part. I don't set prices for any of these molecules, but it is a potential advantage for plinabulin.

Dr. Birnholz:

Certainly, especially when we consider the cost of current biologics, which are very, very expensive, and the cost on both to the patients and to the healthcare system in general, that can be pretty significant.

Why don't we turn then to the clinical trials themselves and start with the Phase II trial that was completed recently. What were the aims for this investigation?

Dr. Blayney:

Well, again, it was a randomized Phase II trial in non-small cell lung cancer. It was comparing Taxotere at 75 mg/m<sup>2</sup> with Taxotere plus pegfilgrastim or Taxotere with plinabulin. It turns out that the benefit of plinabulin in terms of antitumor effect was better, and the plinabulin had, as I said, less grade 3 and grade 4 neutropenia. The dose of plinabulin and the schedule, the schedule of plinabulin was day 1 and day 8, and the dose was either 30 or 40 mg/m<sup>2</sup> of plinabulin. We have in discussions with regulatory agencies to do some dose exploration in terms of what's the right dose to prevent febrile neutropenia with plinabulin.

Dr. Birnholz:

I'm interested in the efficacy data that came out, and you alluded to that a little bit, but specifically regarding plinabulin's effects on neutrophil counts, what were some of the results there in terms of the efficacy?

Dr. Blayney:

Well, it turned out that patients treated with Taxotere had 35% grade 3 or grade 4 neutropenia. Patients treated with Taxotere plus plinabulin had 3% grade 3 or 4 neutropenia, and both of those referred to the first cycle. That effect persisted in cycle 2, 3 and 4 of Taxotere plus or minus plinabulin. So, in summary, that's a big difference, and it's what prompted us to move ahead and try and confirm that with actually looking at, carefully looking at, daily neutrophil counts in the next trials we're doing.

Dr. Birnholz:

And I'm going to definitely want to know about these next trials, because those are being ongoing. There's an interesting call to action there as far as getting people involved and getting oncologists involved. But with regard to the Phase II, I also understand that this neutropenia prevention effect was observed with other chemotherapies besides docetaxel. Isn't that right?

Dr. Blayney:

We haven't tested in humans any other drug, any other chemotherapy drug, besides docetaxel. There's in vitro data suggesting that cyclophosphamide and cisplatin also have benefit from the plinabulin mitigation of neutropenia, but we don't have human data quite yet.

Dr. Birnholz:

What about the side effect profiles? What was reported there in this trial?

Dr. Blayney:

The major side effect that was reported was hypertension, which occurred around the time of the infusion. Remember, the plinabulin infusion was given over 30 minutes. The hypertension was in the 20-30% range, and it was easily managed with calcium channel blockers and was not a long-lasting problem. The other side effects didn't seem to be much different from Taxotere alone.

Dr. Birnholz:

Now, Dr. Blayney, I want to turn to the Phase III study and talk about that in more detail since, for one, it broadens the range of patient populations and cancer subtypes. As I understand, the Phase II trial looked specifically at patients with non-small cell lung cancer. This Phase III is broadening that. I'd like to find out what patient subtypes are involved, what cancer subtypes, and what the trial is seeking to find and who's being recruited for it?

Dr. Blayney:

So, great questions. I'm also excited about this trial. First of all, as I mentioned, the FDA and other regulatory agencies have asked us to make sure that the dose is correct of plinabulin, so we're doing a combined Phase II and Phase III trial. The Phase II portion of the trial has just opened. We'll look at non-small cell lung cancer. We'll use Taxotere as the chemotherapy agent, and patients will be randomized to either receive pegfilgrastim on day 2 or plinabulin on day 1 at a dose of either 30, 20 or 7.5 mg/m<sup>2</sup>. So, the Phase II study will look only at non-small cell lung cancer, Taxotere 75 mg/m<sup>2</sup>, comparing 3 doses of plinabulin and pegfilgrastim. Once we get the

dose, the lowest dose, that we can see a duration of severe neutropenia effect—so, in other words, the test will be the duration of severe neutropenia—we want to see no difference between filgrastim and plinabulin at our Phase III dose. So, the Phase III trial will use pegfilgrastim on day 2 or the right dose or the Phase III dose of plinabulin on day 1. It will be patients with non-small cell lung cancer, with breast cancer and with prostate cancer. All 3 of those tumor types are well treated with Taxotere at 75 mg/m<sup>2</sup>, and Taxotere is a guideline-recommended therapy for prostate cancer, lung cancer and breast cancer. So, that's what the Phase II, Phase III program will look like.

Dr. Birnholz:

So, Dr. Blayney, how can oncologists treating patients with any of these solid tumor types under investigation potentially get involved in this clinical trial directly?

Dr. Blayney:

Well, I certainly can help refer them along. We're certainly looking for physicians who are experienced clinical trialists, who have an up and running clinical trial program and who are willing to engage both patients and physicians and their teams in treating patients with non-small cell lung cancer, prostate cancer and breast cancer with single-agent docetaxel. I can be the contact. My e-mail address professionally is DBlayney@Stanford.edu, and I would be glad to refer interested clinicians for this program.

Dr. Birnholz:

Well, with those parting comments and that helpful referral, I very much want to thank my guest, Dr. Douglas Blayney, for joining me to discuss severe neutropenia from chemotherapy and ongoing efforts to prevent it.

Dr. Blayney, it was great having you on the program.

Dr. Blayney:

Thanks, Matt, it was great to work with you. Thank you for having me.

Dr. Birnholz:

For access to this and other episodes focusing on emerging cancer therapies, join us at ReachMD.com where you can be part of the knowledge.

Announcer Close:

The preceding program has been a special edition of Project Oncology on ReachMD, sponsored by Beyond Spring Pharmaceuticals. Thank you for joining us.