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PODCAST

Breast Cancer Clinical Trials Should Aim to Prevent Metastases

By Patricia S. Steeg, PhD[1] | July 12, 2012

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CancerNetwork speaks with Patricia S. Steeg, PhD, chief of the women's cancers section at the Center for Cancer Research at the National Cancer Institute in Bethesda, Maryland. Dr. Steeg has recently written a perspective in the journal Nature *calling for a shift in both the types of drugs that are developed for breast cancer and in the way clinical trials are designed and executed.*

The breast cancer field has come a long way. The 10-year overall survival rate, according to a United Kingdom study, has increased from around 51% in the early 1980s to 77% in 2007. Tumors of patients diagnosed with breast cancer are now genetically and histologically characterized to better tailor treatment. We are able to identify a subset of high-risk disease patients who likely need more aggressive treatment, and novel and next-generation treatments to treat aggressive tumors are in late stages of development. But patients whose breast cancer has progressed to metastatic disease are unlikely to be cured or even survive for very long. Dr. Steeg believes that rather than solely focusing on drugs that can shrink existing tumors, we need to develop and test drugs that will prevent not only existing tumor growth, but the spread of cancer, or metastasis.


Patricia S. Steeg, MD

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CANCERNETWORK: *Dr. Steeg, you propose that drug developers should start to focus on preventing metastatic disease rather than stopping the existing tumor from further growth, could you explain the rationale for this?*

DR. STEEG: Certainly. I am a molecular biologist, and I study tumor metastasis, which is the movement of tumor cells from the primary tumor to other sites in the body where they progressively grow. This is the major contributor to cancer patient death. We study metastasis in model systems—usually in mice. We inject mice with a tumor, and like in the human process, it forms a primary tumor, and then it spreads. And what I and many other metastasis researchers have noticed is that we have found a number of drugs that, when given to mice soon after the mice develop a primary tumor, will significantly prevent the development of metastases. Now, if we give that drug later, once the mouse has already developed metastases, it does not shrink them. It doesn't obliterate them. But it will prevent them from developing. And so we see this opportunity to prevent metastases in people. And now we need a clinical trial system that will enable us to test this.

CANCERNETWORK: *Are there examples of these types of drugs that have been developed for either breast cancer or for other cancer types, that you describe, that specifically prevent metastases?*

DR. STEEG: Yes. The metastasis literature has a lot of examples of this kind of work. My own research focuses on brain metastasis in breast cancer—10, 20 years ago, breast cancer rarely went to the brain, and when it did, the patient was usually terminally ill and was given some medication for the symptoms. But now, with better systemic therapy, or therapy that goes through your body, a number of women with metastatic breast cancer are getting their first-line of chemotherapy and are now relapsing with brain metastases. This is particularly devastating because we don't have very good treatments for them and they cause a lot of neurocognitive consequences. In other words they impair mental function, they can cause seizures, etc.

So my lab, again, using mouse models, has developed models for brain metastasis of brain cancer, and we have now published three or four drugs—not in common use in breast cancer—that in the model will meaningfully prevent brain metastasis. One of these is vorinostat. It is a histone deacetylase inhibitor. It is an FDA-approved drug for a different kind of cancer. One of them is pazopanib, also an FDA-approved drug for a different kind of cancer. But our models propose that these drugs may be effective in preventing brain metastasis.

CANCERNETWORK: *Could you briefly summarize your viewpoint about clinical trial design? How are our current clinical trials designed and what do you propose that the field should be doing that it is currently not doing?*

DR. STEEG: This is actually a very simple concept. When a drug is developed today, and this is my understanding as a PhD, it is first tested in phase I clinical trials, and this is a dosing and toxicity study largely. So the dose is escalated. You give more and more of the drug to patients and are looking for side effects because you are looking for a safe dose that may have efficacy. Once you find that dose in phase I studies, you go to phase II studies where you are now looking for a hint of efficacy that this drug actually works. And the main endpoint in these trials is shrinkage of tumors.

So these are patients who have had multiple lines of therapy and already have metastases. And what they are asking this drug to do is to shrink those metastases, and that is exactly what I said these experiment drugs won't do in our mouse models. So, for a drug to move on from phase II to phase III trials the drug either has to shrink those metastases by itself or it has to synergize with the current chemotherapy to make the chemotherapy shrink those tumors even better. The drug then goes to phase III trials, which is the large trial against the standard of care—so will this drug, alone, or with the standard of care, improve patient outcomes? And then it goes for approval to the FDA.

After that, there can be what are called adjuvant trials. Now these are metastasis prevention trials. These are when the drug is finally given to women who don't have metastases already. They usually have either large primary tumors or primary tumor cells that have already moved into the lymph nodes. And we are then asking these drugs to prevent metastasis. However, as you can see, this is a very long process and the only drugs that will get there are the ones that shrunk metastatic tumors back in the phase II and III trials.

So what I am proposing is that we need a detour to test for metastasis prevention. We need to get more drugs into metastasis prevention trials. We need smaller trials that we can conduct more often and start getting some more information. And what I have proposed is really quite simple. And that is, after the phase II setting—so we know that the drug is not too toxic, and we have a dose and we have a hint of efficacy and we know what we can combine this drug with in terms of the normal chemotherapy that the patients are given—what I have proposed are one of two types of randomized, metastasis-prevention phase II trials. And it is a pretty simple concept. For instance, we could take patients who have come in for very early chemotherapy, and the chemotherapy hasn't worked so they will be very high risk for full-blown metastatic disease. They would get standard chemotherapy, and then be randomized to either placebo or this metastasis preventive, this compound we think will prevent metastasis. And what would be the endpoint? It would not be shrinkage of a lesion—there are no lesions. It would be time to the development of a first metastasis.

A second flavor of this trial would be those patients who have limited metastases already and they have been treated with whatever the standard treatment is. These patients are doing OK, but they are at extraordinary high risk for additional metastasis. Again, they would get standard of care and be randomized to vehicle or the metastasis preventive. And here, the endpoint would not be shrinkage of their metastatic lesion. It would be time to development of new metastases. I think if we try these trials we could get a signal that this drug may have efficacy in preventing metastasis, and that could lead to new consideration of these drugs.

CANCERNETWORK: *Sure. So the types of trials that you propose, these have been done with tamoxifen and trastuzumab (Herceptin), at least for breast cancer. Trastuzumab was first developed to shrink tumors in the metastatic setting, so is there something that is unique about tamoxifen and trastuzumab, and can we further develop what you described earlier to prevent metastasis?*

DR. STEEG: Well, we were really lucky with trastuzumab and tamoxifen because those drugs have two abilities. One, they shrink tumors and that is what got them through phase I, II, and III trials. And two, they prevent metastases and that is where they were beneficial in the adjuvant setting. So these drugs do both. But unfortunately, there are not that many drugs that will do both functions—shrink tumors and prevent metastasis. If you think about metastasis, you are talking about the ability of the cell to move, not divide, and so you can imagine that there would be drugs that can prevent a cell from moving and invading through tissue to get to where it is going that necessarily wouldn't have a toxic effect or growth inhibitory effect on those cells. And so my point is that there are probably a large number of drugs out there with these capabilities, but we are losing them in the current clinical trial scenario.

CANCERNETWORK: *I see. I think one of the troubles with testing efficacy of a drug that could potentially prevent metastasis is that it may be difficult to predict which patients and which tumors would spread if they were not exposed to therapy. So initially these trials will have to be pursued specifically in patients that are high risk, is that right?*

DR. STEEG: I completely agree. For breast cancer, we know enough about the molecular biology of progression of breast cancer so we can predict groups of patients who are at very high risk for metastatic progression within what I would call a few years—2 to 3 years. One of those groups would be those patients who come in with very large primary tumors, that just grew too fast and they get up-front chemotherapy, they don't go straight to surgery—this is called neoadjuvant chemotherapy. So they get up-front chemotherapy to shrink that tumor down. There are cases where that up-front chemotherapy shrinks that tumor away to nothing and these patients are associated with very good outcomes. But unfortunately, there are a lot of cases where that up-front chemotherapy does not significantly shrink that tumor and the patient goes to surgery. And those patients are at very high risk in a couple of years for metastatic disease. Now the FDA just issued guidance on doing clinical trials in that neoadjuvant setting but I think a perfect opportunity would be for those patients where that up-front chemotherapy didn't have a profound effect and these women remain at very high risk. This would be this kind of population that would be perfect for these metastasis prevention trials. There are other types of patients that could qualify. And, you know, in other types of cancers this concept could also apply and I think you could identify these patients at high risk.

CANCERNETWORK: *And so the last question. We know that microscopic metastases likely exist before we are able to detect them but we do not yet have the developed tools to detect these yet. Do you think that this needs to happen before this shift to test prevention of metastases drugs comes about?*

DR. STEEG: This is a fascinating question, but no I don't. In the neoadjuvant population, we can now identify these patients that are at very high risk. So for instance, in breast cancer: the neoadjuvant population where the tumor didn't shrink; women who go to surgery and have a large number of lymph nodes with tumor in them, so that tumor has already spread past the primary site and has gotten at least that far; women with limited metastatic disease. And I think we are making progress in finding smaller and smaller deposits of tumors which is going to open its own Pandora's box into "When do we treat?" but I think we can do these trials now with the tools that we have.

CANCERNETWORK: *Thank you so much for joining us, Dr. Steeg.*

DR. STEEG: It was a pleasure.