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T-DM1: Golden Age in HER2+ Breast Cancer?

Kathy D. Miller, MD, Harold J. Burstein, MD, PhD | June 12, 2012

Introductions

Kathy D. Miller, MD: Hello. I am Kathy Miller, Associate Professor of Medicine at Indiana University School of Medicine at Indianapolis. Welcome to Medscape Oncology Insights on Breast Cancer, coming to you today from the 2012 annual meeting of the American Society of Clinical Oncology (ASCO®). Joining me today is Dr. Hal Burstein, Associate Professor at Harvard Medical School and Medical Oncologist at Dana-Farber Cancer Institute in Boston. Welcome, Hal.

Harold J. Burstein, MD, PhD: Hi, Kathy. How are you?

Dr. Miller: I'm great. So tell me, when you think about breast cancer at ASCO® 2012, what comes to mind?

The Big Story: T-DM1

Dr. Burstein: The big story here is the data for trastuzumab emtansine (T-DM1). Part of the plenary session this afternoon is the so-called EMILIA trial,[1] which is the registrational study for T-DM1.This is a very interesting drug because it is an antibody/drug conjugate. Part of the excitement is the data themselves, and another part of the excitement is the fact that this is really the first widely used indication for this whole new class of drugs.

So, what is an antibody/drug conjugate? It is the traditional antibody -- in this case, trastuzumab -- that has been chemically linked to a lethal poison called a maytansinoid chemotherapy. By using a very low dose of the chemotherapy, which is linked to this antibody, they can deliver the toxin -- boom -- right to the tumor. We are seeing incredible data.

What is exciting about this class of drugs is that there are literally dozens of related products now in clinical development, and they hold the promise of giving tremendous cancer treatment without the traditional side effects of chemotherapy.

Dr. Miller: Oncologists who treat patients with lymphoma are probably aware that this is not the first in class of antibody/drug conjugate. They have seen data in refractory lymphoma and refractory Hodgkin disease using the same strategy with an antibody complex linked to chemotherapy that shows substantial single-agent activity in previously treated lymphoma patients and previous bone marrow transplant patients.

Dr. Burstein: You caught me out. You are technically correct, that there is already a US Food and Drug Administration (FDA)-approved drug in this class. But for most medical oncologists, treatment for extensively refractory lymphoma or refractory Hodgkin disease -- which is the indication for this other product -- is very uncommon. So the first antibody/drug conjugate that most oncologists are actually going to prescribe to patients and use on a regular day-to-day basis is likely to be T-DM1.

Dr. Miller: This agent is clearly less toxic, but is it also more effective?

EMILIA: Longer Survival, Fewer Toxicities

Dr. Burstein: That is the core of the EMILIA trial. EMILIA is a study for patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer. To be eligible for the study, patients were required not only to have HER2-positive disease but also to have been previously treated with trastuzumab and chemotherapy. The randomization was to the current FDA-approved regimen of capecitabine and lapatinib, another targeted

combination regimen, vs T-DM1. The principal endpoint was originally progression-free survival. The study was modified midway through to make it larger and to look at overall survival as well.

The data suggest that there is a dramatic difference in progression-free survival favoring T-DM1, and there is an emerging difference in overall survival. Actually, it looks like a clinically compelling difference in overall survival. The *P* value is approximately .0005, but because of the way they parceled out alpha, there are some questions about whether it met its statistical endpoint. That is unlikely to be a real issue because when you look at the data, they are surprisingly positive. This is going to be a very widely accepted drug within a short period.

So, the drug has better efficacy and longer tumor control, and the beauty of it is, it doesn't produce the chemotherapy-type side effects. In the comparison arm, the major side effects were the risks for hand/foot syndrome and diarrhea, but none of that occurred with T-DM1. With long-term exposure to T-DM1, you see some cumulative thrombocytopenia, which is rarely clinically significant. You also see some fatigue and transaminitis.

Here is another big plus for T-DM1: It doesn't make the hair fall out. This is a very different kind of therapy, much better tolerated and more active than some of our existing options for trastuzumab-refractory HER2-positive breast cancer. Right now, this drug is the golden era of research in HER2-driven disease.

Targeting Delivery, Not Just a Molecule

Dr. Miller: It is also a golden era for the approach of targeting delivery, rather than just targeting a molecule.

Dr. Burstein: That is exactly right. We have expected the existing antibodies that we have used in oncology not just to reach the tumor cell, but to actually tweak the tumor cell and do something. The great examples are rituximab and trastuzumab. When you start to think about using antibodies as a delivery system, however, all you have to do is get the antibody to "take you to the right address." You can rely on the toxin to do the heavy lifting, and that rapidly broadens its ability. It is pretty easy to make antibodies that bind to cancer cells. What is hard is to make them bind to cancer cells and do something.

The use of antibodies as delivery vehicles -- you are going to see an explosion of interest in this. There are many compelling layers to this treatment. You need a good antibody; a good, well-tolerated toxin; and a linker that allows the toxin to liberate itself from the antibody and go after the cancer cell. It's not a trivial problem, but it's an exciting one.

Dr. Miller: It is one that looks solvable from the first 2 agents we have in this class.

Dr. Burstein: The technology has been there for a couple of decades, but it has taken a long time to see it come to fruition.

Chemotherapy: How to Do It Better

Dr. Miller: I want to take you back to some older topics, because we still have a lot of chemotherapy questions. At least for the next several years, chemotherapy even in the setting of HER2-positive disease is going to be part of our treatment armamentarium. Several studies looked at whether we could do better with our existing chemotherapy drugs.

Dr. Burstein: You are exactly right. The sexy stuff in breast cancer is all about HER2-targeted biologics, but that is only 15%-20% of breast cancer. For the other 80%-85% of patients, we still rely on chemotherapy for a lot of important tasks. Several important comparative studies, one in the metastatic setting and one in the adjuvant setting from the Cooperative Groups, looked to see whether we could improve how we used chemotherapy.

Dr. Miller: What is the short answer?

Dr. Burstein: The short answer is that the old ways still look pretty good. Old friends are good ones, and they hold up well. CALBG 40502, led by Hope Rugo,[2] compared weekly paclitaxel vs weekly nab-paclitaxel vs weekly ixabepilone (almost all given with bevacizumab because of the way the study was set up) as first-line treatment for advanced breast cancer. The patients typically had HER2-negative tumors because they weren't getting a targeted therapy.

In terms of safety, tolerability, and efficacy, weekly paclitaxel was the winner. Questions might remain about whether the investigators dosed the nab-paclitaxel excessively, because there was a lot of neuropathy. Giving it with the ixabepilone-weekly strategy might not be the best way to administer the drug. But certainly, everything points to weekly paclitaxel being the big winner. Obviously, we have had a lot of experience with that as the backbone of ECOG 2100,[3] and that is going to be the mainstay of our approach for first-line metastatic disease.

Finding the Sweet Spot

Dr. Miller: It also tells us that we can't continue to look at toxicity and efficacy as 2 separate buckets. There is interplay between them. Another trial that will probably not get as much play in the United States is a trial from a Korean group[4] looking at maintenance chemotherapy in the metastatic setting. It is a bit odd to us, because we would typically treat patients until progression or toxicity or some personal reason for that patient to stop therapy. But in many parts of the world, patients receive a fairly arbitrary number of cycles. If the patient is responding, therapy is stopped. Patients are off treatment until they progress.

The study looked at longer durations of therapy in maintenance found improvements in progression-free survival and in overall survival. To do that, however, you need to find that sweet-spot balance between an effective drug and a tolerable drug. When you look at the CALGB study, that is where the 2 new, sexier chemotherapy agents faltered.

Dr. Burstein: You are exactly right about the differences in cultural trends and how we use these drugs. The Europeans typically give 4-6 months of chemotherapy for advanced breast cancer, and then historically have paused to see what happened. The US oncology community tends to treat all patients until progression.

There were some classic trials from the Piedmont Oncology Group 20 years ago, which didn't suggest that maintenance or ongoing chemotherapy helped that much. The Spanish trial raises this question again. There was a suggestion of a survival difference, but the trade-off was a reduction in quality of life. So we will have to think about and weigh these factors with our patients. Perhaps now that we have many more drugs available to us, many of which are better tolerated, it's a question that should be asked again in the United States.

Optimal Regimen for Adjuvant Therapy?

Dr. Miller: Particularly in the United States, we spend a lot of time arguing among our colleagues in different Cooperative Groups about the optimal third-generation regimen in the adjuvant setting. Several trials have now compared third-generation regimens, but they haven't ended the argument. We saw the results from yet another one this year: the NSABP B-38 trial.[5] Are the arguments going to continue?

Dr. Burstein: Not in my mind, but you never know what you are going to get into in a bar fight. In the NSABP B38 study for node-positive breast cancer patients, they compared cyclophosphamide (AC) followed by paclitaxel (ACP, or ACT) vs ACT, piggybacking on some gemcitabine, vs the docetaxel, adriamycin, cyclophosphamide regimen (TAC), which is familiar to almost everybody in the audience.

Dr. Miller: We should be clear that the ACT or the ACT with gemcitabine was dose-dense.

Dr. Burstein: That's correct. It was the every-2-week regimen that the CALGB had piloted. In that study, adding the gemcitabine did not improve on ACT alone. And the results for TAC vs ACT were essentially the same in terms of clinical efficacy, but most of the quality of life and toxicity experience suggests that AC followed by paclitaxel is an easier regimen to give. My core regimen is AC followed by paclitaxel. It has been very hard to beat that.

Studies have now looked at adding gemcitabine, and others have looked at adding capecitabine, and that looks like a winner. We had a related study[6] looking at the FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) regimen with or without paclitaxel, and there, too, the addition of paclitaxel looked to be beneficial. Right now, the core regimen for adjuvant therapy is AC followed by paclitaxel, and I don't see many compelling reasons to try anything else.

To Bisphosphonate or Not to Bisphosphonate?

Dr. Miller: One of the other issues that has come up frequently, and has been cause for a lot of arguments in the field in the adjuvant setting, is "to bisphosphonate or not to bisphosphonate." We have seen more data and more meta-analysis trying to parse subsets in this area, with particular interest shown, perhaps, in the estrogen-deprived patients, the postmenopausal patients on an aromatase inhibitor, or the premenopausal patients who get ovarian suppression. Are you swayed by the most recent parsing?

Dr. Burstein: I'm still trying to understand the literature well enough to feel strongly one way or the other. In the modern era, several reports have now looked at adjuvant bisphosphonates, such as zoledronic acid or clodronate. We saw some of this in the past year. For the most part, the aggregate results of the top-line studies have been negative. The one exception is the ABCSG-12 trial,[7] which gave ovarian suppression and endocrine therapy with tamoxifen or an aromatase inhibitor, with or without zoledronic acid, to young women who were not receiving chemotherapy. That study still shows a survival advantage favoring zoledronic acid.

But the AZURE trial,[8] which had a very similar design, using zoledronic acid or not in a larger group of patients, did not show a survival advantage. So, people have been trying to figure out whether meta-analysis or subset analysis could help us. What we saw at this meeting was a subset analysis from AZURE, which suggested that the older, probably postmenopausal, women were most likely to benefit from bisphosphonates.

The argument is that perhaps there is an interaction between the estrogen environment and the role of bisphosphonates in promoting bone health, or in some other way that affects the hormonal milieu such that the cancers are less likely to grow. At the moment, I find myself intrigued, but not persuaded, by these data. I wish that we could have a cleaner analysis. The investigators didn't look at estrogen levels. They used age and menopausal status as surrogates for estrogen level in the same way as in the ABCSC-12 trial. They presumed that all these women had low estrogen levels because they received ovarian suppression with the gonadotropin-releasing hormone agonist, but we don't actually know that.

The verdict is still out. Having said that, we are becoming much more aware of the importance of bone health and checking bone density every year or 2, and our threshold for initiating treatment in women who are estrogen-deprived probably gets lower in part because we are thinking about this more.

Dr. Miller: We may be cheating a little -- perhaps not willing to say, "Yes, I am doing this for adjuvant therapy," but maybe looking for a better reason to give bisphosphonates. And if it helps in the adjuvant setting, that's a bonus.

Dr. Burstein: We are always trying to weigh benefits, risks, and trade-offs. If you can tilt things a little bit one way or the other, it makes you feel better about the choices.

Dr. Miller: Thank you, Hal, and thanks to you, our audience, for joining us in this edition of Medscape Oncology Insights. This is Kathy Miller, at ASCO® 2012.

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