

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
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DR. ERIC WINER: So, our first two moderators are Jeff Abrams from the NCI -- I'll make the introductions shorter now -- and Laura Esserman, who's professor of surgery at UCSF. And they will chair the first session on overview and issues related to breast cancer preoperative therapy.

DR. LAURA ESSERMAN: Good morning. It's a pleasure to be here. Our first speaker this morning is Dr. William Wood, who is the chair of surgery at Emory University, as well as the chair of the Breast Cancer Intergroup of North America. And we look forward to hearing him give an overview of preoperative therapy.

DR. WILLIAM WOOD: Thank you. I wanted to thank Jo Anne for organizing this, and the two of you who've gone to all the effort of sending all those emails around the country to make it happen. I appreciate all that's involved in pulling off something like this. Thank you very much.

I won't spend a lot of time on terminology, but others had. It's been interesting to see the effort that has gone into trying to name preoperative therapy, from "neoadjuvant", "basal" chemotherapy; Jim Holland, "induction chemotherapy"; Vince DeVita wanted to call it "primary chemotherapy". I think the great English Poet will have succeeded in "preoperative therapy" now after this conference, being the name that is given to this approach.

The origin of preoperative therapy was to shrink inoperable cancers to allow surgical extirpation. And this was done initially with endocrine therapy. And then when cytotoxic chemotherapy became available, it was used for both locally advanced and inflammatory breast cancer. The remarkable thing was that it seemed to be very, very effective.

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And, for the first time, you are seeing survivals at 10 years in the 20 percent ranges, whereas previously 20 percent had been the three-year survival in series of patients treated for disease this advanced. It was such a dramatic improvement that it was never prospectively compared to other methods in a randomized fashion.

The response rate, as Dr... as Cokie Roberts has already pointed out, seemed directly related to survival in these series. And the outcome of response raised the question, are we actually, by producing response, achieving these results? Or is the response simply a sorting technique for picking out the biologically most sensitive tumors? And that was a question yet to be answered.

The rationale for preoperative therapy in Stage II breast cancer arose in Milan. Gianni Bonadonna was using induction chemotherapy for Stage II breast cancer to allow breast-conserving therapy. At the time, in Milan you had to have a 3 cm or smaller tumor to have breast-conserving therapy. He was seeing people with larger tumors whom he would be treating with CMF. And, so, he began giving CMF preoperatively.

And the second, putative advantage was to hasten the treatment of micrometastases. The thought was, that by eliminating them prior to the growth spurt that takes place after removal of the primary, which had been described in experimental tumor systems, one might gain an additional advantage.

In some of the early papers on preoperative therapy, Brock's paper was cited. It was a rat Shay chloroleukemia -- a far cry from breast cancer -- but it did make the point that if you operate alone, you had a 10 percent cure rate. With chemotherapy, you could triple that. If you combined them, you could get to 50 percent of the rats surviving. But if you pre-treat it, if you begin the cyclophosphamide a week prior to the surgery, you could usually cure this disease. And the hope was that that would be seen in people with induction chemotherapy.

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Gianni [Bonadonna] published a series of 94 patients that he treated with resectable tumors over 3 cm in diameter. Most of these were treated with CMF initially, then CAF. And he converted almost 90 percent to breast conservation by this technique.

He also pointed out that the response to preoperative chemotherapy predicted prognosis. Gabe Hortobagyi had published this, Namer has, Jacquillat -- others had made the same observation. But, of course, the question was, is this biologic staging or is this causative? And only randomized trials would answer it.

And the NSABP, as they often have, stepped up to the plate with a large, clean, simple design that could address this question. And in the B-18 trial that has so influenced all of our thinking, they had surgery followed by AC, or AC followed by surgery, with tamoxifen for women over 50.

And as you all know, those survival curves absolutely superimpose. So, that it was clear from B-18 that there is no survival advantage from the preoperative timing of chemotherapy. It was also clear that there is no survival disadvantage from leaving the tumor in place while preoperative chemotherapy is administered.

The EORTC was running a trial addressing the same question in another population of 700 patients, to give us the reassurance that in a totally different population the same principle's obtained.

This last summer, the Early Breast Cancer Trialists' Overview presented preliminary data from 11 randomized trials of 5,000 women. Now, this was mostly CMF chemotherapy again -- this was not contemporary chemotherapy. But there were 18 percent fewer mastectomies. In the preoperative arm, there appear to be three percent more in-breast recurrences at five years. Now, these are tentative results -- they need to be confirmed.

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But it would give, even with early chemotherapy, about a 15 percent net gain in breast sparing. And there was no significant difference in recurrence, breast cancer mortality, or death. Here is “any death” -- and you see it’s absolutely null for all these trials. And here are some that are familiar survival curves. Again, no difference between the two approaches.

Now, if we step back a giant step and say, what are our goals in treating anyone with breast cancer? Our first goal -- the one which must never be traduced by any of the other goals -- is, no recurrence of the cancer. Happily, more and more we achieve that goal.

And then the other goals come into play: No evidence of having had breast cancer is extremely desirable for those women who are surviving it. No evidence of having had treatment for breast cancer is also extremely favorable and important. No acute toxicity of the therapy is highly desirable. And no late sequelae of the therapy is very important. And with sentinel node mapping, we were able to do much to have less sequelae from the treatment. It also introduces questions that we’ll address today in terms of timing when we use preoperative therapy. Should we do the staging early or late?

The other, very important lesson from B-18 was that about 80 percent of the patients had shrinkage of their tumor by greater than 50 percent of its diameter, and more than a third had a complete clinical response.

And from that, two important things:

First, if we’re going to do preoperative therapy, it’s essential that at the time of diagnosis, that a clip be placed in the center of the tumor, so that when one goes back to excise this, one can find out if there really was ablation of the tumor, or simply a diffusion of the tumor to that where it’s not easily found.

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The other important thing is that in that 80 percent of patients, women who would've had a significant divot from their breast removed in order to do their lumpectomy can be left with no obvious sign that they had actually had breast cancer. Even with biggish tumors, it's possible in 80 percent of these women to have breast-sparing surgery without any obvious sequelae.

Now, surgery first is, of course, an accident of history. We, as surgeons, were those who made the diagnosis and first treated the patient. And therefore, the idea that surgery was the first thing to be done really is a historical accident.

Preoperative therapy allows:

--> Reduction of tumor volume for cosmesis.

--> The identification of those tumors that are resistant to therapy -- not that we have any idea what to do with them once we've identified them -- but it's a wonderful and fruitful area of research that we'll be talking about.

--> Trials of biologic and other agents can be used as part of the induction so that we can assess this biologically with the surgical and core biopsies, and

--> It favors tailored therapy and the new generation of trials that are beginning now.

So, who should get preoperative therapy? I believe anyone who will require the systemic therapy in question with certainty is benefited by receiving it upfront. This will help us get away from "one size fits all" therapy. Thank you very much.