

NCI 2007 PRE-OP THERAPY IN BREAST CANCER  
16 SESSION 2 TALK 6 - IAN SMITH

DR. NANCY DAVIDSON: Thanks very much. We're going to close out this session going back to a biological target with Ian Smith who's going to tell us about preoperative endocrine therapy.

DR. IAN SMITH: Thank you. The concept of preoperative hormonal therapy is not a new one. And the first paper that I'm aware of was published back in 1957; and there have been a whole series of similar phase 2 studies which I'm not going to spend too much time on this afternoon because in recent years there have been some randomized phase 3 trials where the data, I think, are a lot more secure.

So, the first question I want to ask with this is, how effective is preoperative hormonal therapy in achieving tumor regressions and in down-staging to avoid mastectomy?

There are four double-blind multi-center trials that have been carried out recently all involving aromatase inhibitors and all dealing with post-menopausal women; and there are also two smaller trials which I'll mention briefly.

So, the first is the [NSABP-]B-24 preoperative tamoxifen versus letrozole trial that was published by Dr. Eiermann and updated by Matt Ellis; and you can see the details. There are four months of treatment; none of these patients were suitable for conservative surgery. One of the points I wanted to make in comparing these trials is that the criteria for entry was slightly different. Now, the clinical response rate -- you can see in the second line -- now there was a significant benefit in favor of letrozole; there was also significant benefit in favor of ultrasound response.

I'm not going on and on saying this, but all these trials show that if you use ultrasound as a measure of objective response, you get the same qualitative difference; but, in general terms, the actual response rates are lower.

PRE-OP THERAPY IN BREAST CANCER  
16 SESSION 2 TALK 6 - IAN SMITH

And then in terms of breast-conserving surgery -- the bottom line -- again, there was a significant benefit in favor of letrozole.

In the IMPACT trial in which I was involved -- this was tamoxifen versus anastrozole versus a combination. For reasons that I'll explain later, and we'll also hear more about tomorrow, this trial was designed exactly to mimic the ATAC trial; so this is, in a sense, neoadjuvant ATAC.

But the median tumor diameter was smaller here than in the first trial I've shown, and, in fact, almost half the patients were suitable for conservative surgery. And here, there was not a significant difference in overall response rate between any of the three arms or in the ultrasound data. There was, however, a benefit for anastrozole in terms of breast-conserving surgery; and you may see these dates are a little bit, you know, "How does that work?"

Well, I think probably it's something to do with the fact that small tumors treated with neoadjuvant endocrine therapy regress slowly and they're actually quite difficult to measure accurately. That's not a very subtle scientific hypothesis, but I think that may be the explanation.

Another trial, the third, which, again, compared tamoxifen with anastrozole -- PROACT. Now, this trial had the problem -- I would use the word, "problem"; I think it's appropriate -- in that quite a lot of the patients had chemotherapy as well -- that clearly makes interpretation rather difficult.

But 330 were endocrine-therapy-alone, and, again, this dealt with larger patients... larger tumors. Maybe the patients were larger as well because I think this was done in the States. (Laughter) Am I allowed to say that? Shall I go now? (Laughs) So here, again, there was not a significant benefit in favor of anastrozole -- although there was a trend --

**PRE-OP THERAPY IN BREAST CANCER  
16 SESSION 2 TALK 6 - IAN SMITH**

and in terms of breast-conserving surgery, again, as in all the other trials, there was a benefit in favor of the aromatase inhibitor.

And then, finally, a small trial comparing exemestane with tamoxifen -- and just to confuse you, the data read down the way here -- and you can see in this small trial that exemestane was clearly superior to tamoxifen in terms of overall response rate, in terms of ultrasound response, and, again, in terms of breast-conserving surgery.

So what you can say with these trials is, around about 50 percent of patients -- maybe slightly less than that -- were responding. That the aromatase inhibitors in some, but not all, the trials did better than tamoxifen. They always seem to do better in terms of breast-conserving surgery, which, clinically, seems to me to be the main point of doing these studies.

This is a trial [ACOSOG-Z1031] which is running -- I don't have any update on it -- comparing the three aromatase inhibitors head-to-head, just for your information.

Now the next question is: is preoperative endocrine therapy as effective as chemotherapy? I don't actually think this is a very sensible question to ask. I think what we're looking for nowadays is trying to find out which patients are going to benefit best from which treatments. There is only one small study, as far as I'm aware, and the data are possibly not what you would expect, showing very high response rates for the two neoadjuvant endocrine agents and a rather low response rate for neoadjuvant Adriamycin-Taxol.

And, again, for breast-conserving surgery, the endocrine therapy beat the chemotherapy. Well, clearly these data have to be repeated, but I think at the very least it makes the point that we don't just need as a knee-jerk to go straight into neoadjuvant chemotherapy when we see a middle-aged or older patient who's got a large estrogen-receptor-positive breast cancer.

**PRE-OP THERAPY IN BREAST CANCER  
16 SESSION 2 TALK 6 - IAN SMITH**

Now, if you look at the IMPACT trial versus the letrozole trial, these are the response rates of the two endocrine... of the two aromatase inhibitors, which might suggest to you that letrozole was better -- all these are non-compared data. But, in fact, with the 223 Trial -- that I'm going to tell you about in a minute -- the response rate to anastrozole was higher. And this was done by the same group of patients using largely the same entry criteria -- in other words, done by the same group of investigators, rather. So it raises the question: what is the optimal duration of endocrine therapy? Because the difference between this trial and this trial is that we went on for longer.

Well, there's not a lot of good data on this. There is a UK study -- it dates back a bit now -- called the Golden Oldies, and these patients were all over 70 and the design of that trial was tamoxifen alone versus surgery and tamoxifen. And the bottom line of that trial is that there was a significantly higher local relapse rate with tamoxifen alone than with surgery, and in the long-term -- it took a long time to emerge -- there was, in fact, a worse mortality.

So the message is, you certainly can't go on forever, and neoadjuvant endocrine therapy - - at least in most patients -- has to be for a finite duration before surgery kicks in.

There are some data that Mike Dixon has shown me that he's planning to publish in 63 patients on letrozole for more than three months, and this shows that there is a steady, slow increase in the response rate. And this shows the time to treatment failure. You'll see that the first failure starts just around about a year, but the great majority of patients are continuing out to two years or more.

So, you can get continuing responses for up to two years in some patients. And it's axiomatic that longer duration is going to perhaps increase the breast conservation chances if you're getting further response. The optimum duration is not yet clear -- it

PRE-OP THERAPY IN BREAST CANCER  
16 SESSION 2 TALK 6 - IAN SMITH

may very well vary for different patients; but the key point is, it's not a long-term substitute for surgery unless there's some strong medical contraindication.

So, which patients are most likely to respond to preoperative endocrine therapy? Well, Matt Ellis from the P04 trial -- P024 trial -- published data that suggested that the response related strongly to the ER quantitative level, based on the Allred score, and, at lower levels, there were only responses with the aromatase inhibitor but not with tamoxifen. The numbers here are small.

When we looked at our own results in the IMPACT trial, overall, there was a correlation with the quantitative level -- this is H-Score -- in that the two higher levels there was a higher response rate than the lower levels. Now that's total. When we looked at response by treatment relating to Allred score, there wasn't any superiority for anastrozole, which are the purplish lines, over tamoxifen. As it happened, there was significant benefit relating to higher scores for the combination. Our explanation for that is that it's just one of life's coincidences, but there may be another.

Now, this is a slide that I've hawked around the world, and it shows that both in the letrozole P024 trial and in the IMPACT trial, there is a really major benefit in favor of the aromatase inhibitor for the HER2-positive tumors. In the letrozole trial, it was highly significant. In ours, because the numbers were small, it wasn't significant; but -- you're not supposed to say numerically -- but, numerically it looked impressive.

These data have not stood up to the equivalent adjuvant trials. And this shows the BIG-198, which is letrozole versus tamoxifen. These data were presented by Giuseppe Viale at San Antonio. And you'll see that the benefit is the same -- no greater -- depending whether you're HER2 negative or HER2 positive. And Mitch Dowsett at last year's San Antonio presented similar data from the ATAC trial and again there is no selective benefit in favor of the aromatase inhibitors for HER2 positive versus HER2 negative. If anything, there's a slight trend going the other way around.

PRE-OP THERAPY IN BREAST CANCER  
16 SESSION 2 TALK 6 - IAN SMITH

So can neoadjuvant endocrine therapy provide short-term surrogates for long-term outcome? That's one of the key cornerstones of why we're doing all this. Well, if you look, first of all, at clinical objective response, the data are not all that convincing -- the P024 trial, yes. It predicted for the outcome of BIG-198. Letrozole was better.

The IMPACT trial did not predict for the ATAC trial. The PROACT trial did not predict for the ATAC trial, although the PROACT trial did show quite a strong trend. And as I've just shown you, in the HER2 positive subset, neither the P24 nor the IMPACT trial did the neoadjuvant findings predict for the adjuvant findings.

So it does, in endocrine therapy, at least, raise a big question mark, I think, over the predictability of clinical objective response for long-term outcome.

Well, pathological complete remission -- this is quite easily dealt with. You just do not get pathological responses very commonly -- complete remissions, rather -- in these neoadjuvant trials -- 0.5 percent, none in the... I'll tell you about this trial in a minute -- and 1.5 percent in the P024 trial.

So what about molecular endpoints? Well, this is going to be dealt with in detail tomorrow by Professor Dowsett. But I just want to make one point just now, which is in the IMPACT trial, although there was no benefit from clinical response, nevertheless, the reduction in Ki67 was greater for anastrozole both at 2 weeks and at 12 weeks -- was greater than either tamoxifen or the combination. So this, of course, did predict exactly for the outcome in the ATAC trial. So that made us feel that change in Ki67 -- or 2-week Ki67 -- may be a more relevant endpoint than clinical response.

Now, in the patients who had anastrozole, I just want to illustrate something: these lines are for individual patients. Here's the start, this is what the Ki67's doing at 2 weeks, this is what's happening at 12 weeks -- and you can see there are at least three different

PRE-OP THERAPY IN BREAST CANCER  
16 SESSION 2 TALK 6 - IAN SMITH

groups here. The purple ones do well; the blue ones do not do well -- there's not much switch off; and the white ones respond briefly but then seem to escape. And we hypothesized that perhaps with cross-talk between signal transduction and the estrogen receptor, that signal transduction inhibitors might somehow overcome this molecular resistance.

So we did a trial with gefitinib, Iressa -- a neoadjuvant trial -- using Ki67 as the primary endpoint. And gefitinib was started after 2 weeks to allow us to see, overall, whether there was a benefit, and also to allow us to see if the less responsive patients, as defined by Ki67 at the 2-week mark, might perhaps benefit from gefitinib.

And just the brief bottom line of the results is that the addition of gefitinib to anastrozole did not enhance the effect as measured by reduction in Ki67. This is the combination, and there was a numerically greater effect with anastrozole alone. And in terms of objective response, neither in the initially sensitive patients -- these are the patients whose Ki67 dropped after 2 weeks -- nor in the initially less sensitive -- these are the patients whose Ki67 did not drop significantly after 2 weeks -- in neither case was there any benefit from adding in the gefitinib -- and, if anything, it was a trend in the opposite direction.

I show these data partly to demonstrate how I think you could go using neoadjuvant trials as a prelude to adjuvant therapy. And certainly these would not encourage you, I don't think, to set up a large adjuvant trial with anastrozole and gefitinib.

And the very final point I want to make is: can short-term molecular endpoints predict for long-term outcome in the individual patient? Again, this is going to be dealt with in more detail tomorrow.

But just to make the point that when we looked -- we've now got a lot of follow-up -- up to more than six years in some patients in the IMPACT trial -- and when we looked at the

**PRE-OP THERAPY IN BREAST CANCER  
16 SESSION 2 TALK 6 - IAN SMITH**

log Ki67 at baseline divided by tertiles, there was a significant difference, only just, between the three tertiles. This is not new -- other people have shown the same. But when we then looked at the effect after 2 weeks, there was actually quite a striking difference between the three tertiles.

And the hypothesis, therefore, is that you might be able to use the 2-week Ki67, which is a very simple immunohistochemical test -- you can do it just as easily as estrogen receptor -- at least I can, Professor Dowsett can -- just as easily as estrogen-receptor and so on -- after you do a short duration of anastrozole.

You might just say that this group perhaps don't need anything else, but this group do, and you can make your judgment here. So if this were true, then a simple test 2 weeks after starting an endocrine agent might tell you whether you needed to add in more therapies or not.

And on the basis of that -- and Mitch is going to spend a lot more time on that tomorrow - - my last slide is a UK POETIC trial. This stands for "PreOperative Endocrine Therapy Individualizing Care". And patients are going... This is a large trial -- it's going to involve 4,000 patients. Patients will be post-menopausal, hormone-receptor-positive as determined by core biopsy, and they will be randomized either to standard treatment, which will be surgery and then standard adjuvant therapy, or two weeks of preoperative neoadjuvant aromatase inhibitor and then surgery and then standard adjuvant therapy; so this is the experimental bit. And we want to ask two questions: first, is it possible that preoperative endocrine therapy might enhance long-term outcome? There are experimental data that suggest it might. It's never been addressed. You heard this morning about neoadjuvant versus adjuvant chemotherapy trials; but nobody's done it for endocrine therapy.

But the other point is to see whether the 2-week Ki67 after treatment will indeed -- in other words, to validate the data I've already showed you. And also to look at a whole



PRE-OP THERAPY IN BREAST CANCER  
16 SESSION 2 TALK 6 - IAN SMITH

host of gene expression array changes, which might be very valuable in helping us to predict which patients need further treatment and which patients will do well on their aromatase inhibitor therapy alone.

So just to summarize: Aromatase inhibitors are more effective than tamoxifen as neoadjuvant treatment, both in terms of response rate and in terms of breast conservation. So there's a nice, easy message there that if you're trying to conserve the breast, you're basically better off using an aromatase inhibitor.

The optimum duration is uncertain; but I think at least four months and probably more. And I think those of us -- and I'm as much to blame as anyone -- doing short-term, short-duration, three-month treatments are probably not enough if you're trying to reduce tumor size to avoid mastectomy.

This treatment's well worth thinking about instead of chemotherapy in older patients with strongly ER, PgR positive cancers; and the trick, of course, is to work out which patient should get which -- how to select, in other words.

And, finally, clinical response is not a reliable surrogate for long-term outcome. Pathological complete remissions are too rare to be any use here. It's a different ballpark from chemotherapy.

And molecular markers, including, I think in particular, after short-term therapy -- short-term preoperative -- which I think is where we should be putting most of our resources [re: molecular markers]. Molecular markers after short-term treatment may be the way forward in telling us which treatments are going to work best for the individual patient. Thank you very much.