NCI 2007 PRE-OP THERAPY IN BREAST CANCER
11 SESSION 2 TALK 1 - WOLMARK

DR. NANCY DAVIDSON: We're going to start with a talk by Norm Wolmark, who's going to update us about -- it says "The American Experience", Norm -- on preoperative chemotherapy. I believe this is very updated, in that it just came through over the last 24 hours, is that right? So, this is new and to the point. Norman.

DR. NORMAN WOLMARK: Thank you, Nancy. Thank you for disclosing our methodology. (Laughter) You know, slides by the close of business three weeks ago when we really get the life-table analyses yesterday…

So, I really don't propose to speak about the "American" experience. I'm not sure it's desirable or appropriate to emphasize our regional differences for a disease whose ravages really don't recognize borders and nationalities and delivers its suffering in a uniform and unbiased manner. What we have, however, been asked to do by the meeting organizers is to update the data from NSABP protocol B-18 and B-27; and that we plan to do.

So, for surgeons to have embraced preoperative therapy, two prerequisites had to occur. One was the retreat from radical mastectomy. Whenever one has the temerity to mention "radical mastectomy" or challenge its sanctity, it is always appropriate to pay homage to William Stewart Halsted, who is shown here in a rather unusual pose, showing some hitherto undisclosed humanitarian features, such as his love of dogs and puppies. (Laughter) Perhaps we'll pick up on this canine theme later on in the presentation, if time permits.

But I think the retreat from radical mastectomy had to play a pivotal role, for surgeons to embrace preoperative therapy. And the NSABP contributed to this retreat from radical mastectomy. The data from B-06 were published in 1985.

And, of course, the surgeon, if he or she embraces this concept -- the concept that a standard of care represents breast-preserving operations -- invariably comes face to face

with his or her most daunting nightmare: do we now look upon and challenge the primacy of the operation? Do we now regard the operation -- the sanctity of the operation -- as being relegated to a secondary role? Secondary to a more dominant intervention that becomes the principal intervention, such as, perhaps, chemotherapy -- preoperative chemotherapy -- or chemotherapy with a biologic?

How do surgeons deal with nightmares? (Laughter) Well, Ambien certainly is a quick fix (Laughter); but on the other hand, I think that surgeons dealt with this dilemma in a definitive and courageous way by participating in randomized, prospective clinical trials a priori designed to challenge the dominance of the operation in the treatment of Stage I and II breast cancer.

The second prerequisite that was necessary for surgeons to embrace preoperative therapy was the demonstration of the efficacy of adjuvant chemotherapy both in node-negative and node-positive patients. And in 1988, when the NSABP started B-18, four cycles of AC appeared to fulfill this prerequisite, in that it demonstrated prolongation of survival in both node-negative and node-positive breast cancer.

So with this, the NSABP embarked on a series of protocols. B-18 testing pre-operative AC versus post-operative AC, 1,500 patients randomized. B-27 started where B-18 left off, to determine whether adding four cycles of Taxotere to the AC would improve and downstage the effect on the primary tumor and the lymph nodes. And NSABP protocol B-40, which was just initiated November of '06, which tests the intervention of a biological, bevacizumab, in this preoperative setting, using pCR as an endpoint.

So, the data: NSABP protocol B-18. The diagnosis was made with core biopsy or fine needle aspiration; vulneration of the breast with an open biopsy or excision was prohibited. And patients were randomized to what we now, as of this meeting, call the "accidental" sequence (Laughter) -- operation followed by four cycles of AC -- or the

experimental sequence -- the test of the primacy of the operation -- four cycles of AC followed by the operation.

As was stated previously, tamoxifen was restricted only to those mature women who were over 50 years of age; whereas women under 50 years of age did not receive tamoxifen. The trial was open October of 1988 and completed in April of 1993 after 1,523 women were randomized.

Now, the real update for this presentation is B-18, because the last time we disclosed the results from this trial was in 2001 at an NIH Consensus meeting. And we published the data in the *JNCI* monographs of that same year with a mean time on study of 9.5 years. We now have an additional 6.5 years of follow-up.

Do the conclusions made in that 2001 monograph stand the test of time?

This was a population that was not locally advanced, as we see by this distribution of tumor size -- 28 percent had tumors under 2 cm, 60 percent had tumors between 2 and 4 cm; 74 percent of this cohort was clinically node-negative. So what was the tumor response for four cycles of preoperative AC?

Am I too loud? (Laughter) I feel the audience is withdrawing from me. (Laughter)

So, tumor response with four cycles of preoperative AC -- he said sotto voce. (Laughter) Well, 79 percent of the overall cohort had an objective clinical response; 36 percent had a complete clinical response; and 13 percent had a pathologic complete response, with an asterisk -- because approximately 25 percent of all our pathologic complete responders had residual non-invasive cancer, and rather than splitting histograms, which are sort of like large hairs, (Laughter) I will not belabor this time and time again.

There was nodal down-staging -- clearly -- that was statistically significant: 42 percent of the accidental -- standard -- group had -- 42 percent -- negative nodes, compared to 60 percent in those women who received four cycles of preoperative AC.

Moreover, those individuals who received the standard sequence had 60 percent breast-preserving operations, compared to 68 percent for those individuals who had the chemotherapy given preoperatively.

And, ladies and gentlemen, saving the breast is a noble endeavor, which is achieved by preoperative chemotherapy.

What about outcome? This is a slide that we showed in 2001 which has been shown time and time again, and has been shown by Bill Wood and Gabe Hortobagyi in their introductory remarks. And we said that it really didn't matter whether we gave the four cycles of AC preoperatively or postoperatively, that the results were the same relative to disease-free survival and overall survival.

Is that still the case with 6.5 years of additional follow-up? Well, there is no statistically significant difference. On the other hand, one sees a trend that favors the preoperative group. Moreover, it seems that these curves are separating at five years. So, we went ahead and did an unplanned analysis, a conditional probability for those individuals who are alive and disease-free at five years, to determine what their subsequent risk was for the next 10 years.

And here we see that if we do this exercise, we see a statistically significant advantage in favor of the preoperative group relative to disease-free survival from Year 5 to Year 10 -- the hazard ratio's 0.81 with a p-value of 0.05.

On the other hand, when we examine survival, these curves still remain inextricably intertwined, with a negative p-value.

There's something disquieting about these data that dates back to the analysis of 2001. John Bryant, who tragically died in September of 2006 of metastatic parotid acinic cell carcinoma, was concerned -- and I was concerned as well -- on that 2001 analysis, that there could be a treatment-by-age interaction. It was around 0.04, so we didn't really emphasize it -- although we did discuss it in that *JNCI* monograph paper in 2001.

So, let's revisit the issue: treatment-by-age interaction. If we now look at disease-free survival for young women --under 50 years of age -- we see there's certainly a trend in favor of preoperative chemotherapy compared to postoperative chemotherapy -- hazard ratio of 0.05 (correction: 0.85), p-value 0.09. There is no such trend in more mature women, who are over 50 years of age, where there is superimposability of these two lines.

This trend for women who are under 50 years of age becomes more marked when we examine overall survival, where here we, again, see that it appears that those individuals who receive preoperative chemotherapy have a better overall survival than those who receive postoperative chemotherapy -- p-value 0.06, hazard ratio 0.81.

Whereas those women who are over 50 years of age seem to have the opposite trend, in that those individuals who received post-operative AC appear to have a trend for superiority compared to the preoperative group -- a hazard ratio of 1.23, a p-value of 0.07.

The formal test for interaction, which in 2001 was 0.04, is now 0.01. So, we seem to have a qualitative interaction: whereas the younger women appear to sustain a greater benefit from preoperative AC, the older women -- the more mature women -- seem to have a benefit from postoperative AC.

Now, when we speculated on the reason for this, we stated that it was enigmatic when the p-value was 0.04. At this point, we can only conclude that it is more significantly enigmatic (Laughter) than it was when we first reported the data in 2001 -- certainly food for thought.

And I apologize that we no longer can fit this information into those very pleasant, superimposed disease-free survival and overall survival curves. Gabe, I'm sorry, but them's the data.

What about pCR and outcome? Well, this is the slide that I showed during the last Consensus meeting, showing that those individuals who achieve a pathologic complete response have an outcome that's superior -- significantly superior -- to those patients who do not.

Does this association still hold up with the additional 6.5 years of follow-up? And it most certainly does. Highly statistically significant difference in those individuals who achieve a pathologic complete response compared to those who don't -- a hazard ratio of 0.07 (correction: 0.47), lots of zeros after the decimal place. Our statisticians get an endorphin rush. The 10-year point estimates are 75 [percent] for the pCR group, compared to 52 percent for those individuals who did not achieve a pCR.

These differences extend very clearly when we examine overall survival, where we see point estimates at 10 years that have an absolute 20 percent difference -- 86 percent versus 66 percent -- a hazard ratio of 0.28, a p-value that is highly statistically significant.

So, clearly, this is fertile ground to develop a molecular profile to determine both the benefit relative to pCR and for those who do not achieve a pCR. And, certainly, we'll hear a great deal more about this later on in this meeting. Certainly, Luca Gianni and his OncotypeDX [study], I think, has made a significant step forward in addressing this issue and we will hear from him during the next presentation.

So, B-27 really picked up where protocol B-18 left off. And, in this situation, all three groups received adjuvant (correction: neoadjuvant) chemotherapy. The first group received four cycles of AC just as was given in protocol B-18, followed by the operation. The second group received four cycles of AC followed by four cycles of docetaxel preoperatively, followed by the operation. The third group received four cycles of AC followed by the operation, followed by post-loaded [-operative] four cycles of docetaxel.

For the purposes of this update, I will concentrate on these two groups primarily. Now this was a more egalitarian study than NSABP protocol B-18, because all women received tamoxifen regardless of age or receptor status. Tamoxifen was given concomitantly with chemotherapy with for both NSABP protocol B-18 and [B-]27, according to what was written in Dr. Bear's paper that came out in May of 2006. Is that not correct Dr. Bear? Dr. Mamounas believes that the chemotherapy was sequential. Do we have a show of hands? Very well.

Between December of 1995 and December of 2000, 2,400 women were randomized into this study. Dr. Bear's paper in *JCO* in May of 2006 had a mean time on study of 6.5 years -- we now update this to 8.5 years.

And, again, the distribution of clinical parameters for NSABP protocol B-27 indicates that this was a group that had a larger proportion of larger tumors, in that 45 percent of the cohort had tumors that were over 4 cm, compared to B-18, which was 13 percent, and had a somewhat lower proportion of clinically node-negative disease.

So, what was the tumor response with AC compared to AC followed by four cycles of Taxotere? That with AC alone, we see exactly the same pathologic complete response that we saw in NSABP protocol B-18. With the addition of four cycles of Taxotere, this was doubled to 26.1 percent, with a highly statistically significant p-value. So, adding the four cycles of taxane doubles the pCR rate.

There was also significant nodal down-staging, in that the four cycles of AC had 51 percent of the patients who were histologically node-negative, and this was raised to 58 percent for those who received the additional four cycles of taxane.

That the association of pCR was independent of the clinical nodal status. It was independent of tumor size and independent of patient age. It was also independent of estrogen receptor status -- that we saw a proportionate increase that was similar whether the patients had tumors that were ER-negative or ER-positive or ER-unknown. Yes, there is a lower incidence of pCR for those who are receptor-positive; but, nonetheless, the addition of taxane certainly improved that pCR to a same degree, or more, than for receptor-negative patients.

This is also true for lobular carcinoma in situ, which had a lower pCR rate; but the proportionate increase with taxane was similar regardless of histologic subtype.

There was a strong association between pathologic complete response in the tumor and pathologic complete response in the axilla. If we develop a tumor pathologic complete response, only 13 percent had positive histologic nodes, compared to 50 percent for those who did not achieve a pathologic complete response in the primary lesion -- a very strong association.

Well, what about outcome? Disease-free survival, now updated for the additional two years -- that we see that this is not statistically significant, despite the fact that the pCR was doubled. We see a trend in favor of the AC followed by Taxotere; but, again, the relative risk is 0.92.

On the other hand, if we look at recurrence-free survival or relapse-free survival -- and this was not a pre-planned analysis -- and RFS excludes second primaries and primaries of the contralateral breast -- we see that there is a statistically significant advantage for

the four cycles of Taxotere added to the AC, compared to the AC alone. Point estimates at five years -- 76.3 versus 70.8 percent for the pairwise comparison -- a relative risk, or a hazard ratio, of 0.83 with a p-value of 0.04.

This benefit appeared to be restricted to those individuals relative to local or IBTR -- where we see a significant benefit for the addition of a Taxotere to the AC at eight years, whereas the distant [recurrence] curves seem to be superimposed.

The overall survival for all three groups appears to be, at least to this point -- although we were surprised with the B-18 data following five or six years -- we see, to this point, no separation of these curves: they're absolutely superimposable -- hazard rates of 0.93 and 0.97.

So what about pCR and outcome? Does this apply and does this still hold up for NSABP protocol B-27? And it certainly does. We see a highly statistically significant difference in disease-free survival for those individuals who achieve a pathologic complete response -- and there are twice as many in the Taxotere group as there are in the AC group -- compared to those individuals who do not achieve a pCR, relative to disease-free survival. Point estimates of 85 percent versus 67 percent, hazard ratio of 0.45, highly statistically significant p-value.

This translates to an overall survival benefit. Those patients who develop a pCR: 93 percent overall survival at five years, compared to 80 percent for the non-pCR group -- highly statistically significant and a hazard-ratio of 0.33.

What about this group -- the non-pCR group -- that constitutes 75 percent of this population? They are a heterogeneous group. And, certainly, when we examine the outcome of this group according to histologic nodal status, we see that there is a wide separation between those who have zero positive nodes compared to those who have 10+ positive nodes. And approximately 47 percent of this cohort has zero positive nodes.

Granted, their outcome is not as good as those with pCR, but yet there is a wide range in separation.

So, clearly, developing a genetic profile that predicts outcome both for pCR and non-pCR is highly desirable. Certainly not a matter of age-interaction, it's a matter of the biology of the tumor and interaction with chemotherapy, preoperative or otherwise.

Certainly, the state of the art is being moved forward, as is clearly demonstrated by NSABP-B-40, which has started as of 11/07, which introduces bevacizumab, plus or minus, into this preoperative regimen, aiming for a pCR of 40 percent.

B-41 will, for HER2-positive patients, test trastuzamab, lapatnib, and the combination thereof, now aiming for a pCR rate of 64 percent. If the surgeon was not particularly intimidated by a pCR rate of 25 percent, certainly one of 65 percent will certainly gain his notice without any question whatsoever.

So, then, I think we have a marvelous opportunity to move the state of the art forward using this preoperative setting, where one has access to the tumor as it's being perturbed.

So, I will end by sharing one of my nightmares. (Laughter) And that is, that we have a great opportunity to move the state of the art forward, but we will be judged harshly if we fail to do so. How will a lecturer standing from this lectern look back upon this era? And will they have the desire to show this slide? Thank you very much.