NCI 2007 PRE-OP THERAPY AND BREAST CANCER
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DR. GEORGE SLEDGE: Thank you, Gunter. I must say it's frightening how rapidly some phrases enter the general use in medicine, like "surrogate of a surrogate". It's now my pleasure to introduce to you Dr. Hal Burstein. Hal is at the Dana-Farber Cancer Institute, and is on the faculty of the Harvard Medical School, where he has actively developed several novel biologic agents. He'll be speaking to us today about the pressing question of follow-up after preoperative therapy, including the need for additional systemic therapy. Hal.

DR. HAROLD BURSTEIN: Well, good afternoon. I want to extend my thanks as well to the conference organizers for asking me to join you today. I was asked to speak about what comes after preoperative therapy and, in particular, what comes after preoperative chemotherapy. And, in contrast to Gunter's remarks, the presumption here was that the patient would have already finished what we would consider a standard course of modern chemotherapy. And the most frequent question I get from patients in clinic who have been through neoadjuvant chemotherapy is, "okay, now what?" And that was the topic that we tried to tackle.

So, most of my comments have already been made probably several times by other speakers already today, but obviously the point of all this preoperative therapy is to deliver effective systemic treatment to hopefully downstage the tumor in anticipation of surgery, and to assess the dynamic response to therapy. Of course, this is what particularly distinguishes the opportunities we have in neoadjuvant treatment from adjuvant therapy.

And, at the population level, the goal is to use surrogates or, perhaps as George said, surrogates of surrogates to define the efficacy of novel treatment regimens.

And for individuals, or for patients who are in our practice, what can we learn from preoperative therapy that's helpful down the road? Well obviously we learn something about their prognosis, and ideally we'd like to get to the point where we are then able to tailor treatment programs based on response, and you've heard some very exciting work that the German group and others have been doing on that line.

So what I'm going to briefly speak to are issues of surveillance for women who've had neoadjuvant chemotherapy for breast cancer, and then a discussion about what could come afterwards in the way of systemic treatment options.

Let me say a few words first about local-regional recurrence after preoperative therapy, though this is the topic of an important session tomorrow as well. But, of course, the goal of pre—operative therapy is to surgically downstage the patient, and, as a corollary, we would like to see more of our patients have breast-conserving surgery after preoperative treatment.

There has been the suggestion in the literature that patients who have breast-conserving surgery after preoperative treatment may be at higher risk for local-regional recurrence. And it's clear from reviewing the papers on preoperative treatment that local-regional recurrence does constitute a substantial percentage of breast cancer events in women who've had neoadjuvant therapy, perhaps owing to the higher stage at diagnosis or other clinical choices there made along the way.

In a meta-analysis that was published two years ago in the *JNCI*, they compared overall survival, disease progression, and distant recurrence from the major studies of adjuvant versus neoadjuvant therapy and, as you can see in panels A, B, and C, there was really no

difference whatsoever. However, as shown panel D, in the lower right, there was the suggestion of a slightly greater risk of local-regional recurrence among women who had neoadjuvant chemotherapy compared to adjuvant treatment, for reasons that are not entirely clear.

These are data from the published experience from the NSABP. I, like everyone else has given my royalty check to the NSABP Foundation to get through this talk, and just shown here are the incidence of local, distant, and regional recurrences, just to make the point that in this patient population a substantial fraction of events will include local or regional or ipsilateral breast recurrences in this group of women treated with neoadjuvant chemotherapy, across the board.

However, there are no unique surveillance guidelines for local-regional evaluation after preoperative therapy. And I think that there is no a priori dataset or reason to necessarily change our standard operating procedures in following women after neoadjuvant therapy. However, because of the risk of local-regional events, I think clinicians do have to be aware that standard surveillance may not be enough in all patients, and we should all have a relatively low threshold to further evaluate changes that appear in the chest wall or breast because of the high-risk nature of this patient population.

Well, now what I want to speak to next is really the issue of surveillance and treatment after systemic therapy, and I think it's important to remember that for all these women, neoadjuvant treatment is going to be part of a very long spectrum of multi-disciplinary care. The vast majority of women who are receiving neoadjuvant chemotherapy will additionally receive, of course, surgery, and perhaps radiation therapy, but will also receive additional systemic therapy. The majority will receive anti-estrogen treatments,

and that fraction of women who have HER2 positive disease will also receive anti-HER2 therapy, that is to say trastuzumab, as ongoing parts of their experience.

Now, there are no specific data that I could find in the literature to suggest that there is a different need for a different surveillance algorithm that is currently employed in the routine management of women after treatment for early-stage breast cancer. And, in fact, I could not really find any data on that point. And based on what I think is a consensus with speaking to many of my colleagues, I think many of us would endorse the current guidelines, for instance those promulgated by ASCO for routine surveillance of women following neoadjuvant therapy. Again, there being no specific reason to think to do otherwise. However, again we do have some extra risk information in those women, and it's clear that women who have substantial residual tumor burden, as you heard today, are at greater risk for tumor recurrence, and we have to have a relatively low threshold to evaluate their symptoms based on the prior probability of their developing metastatic disease.

Well, is there a role for additional chemotherapy in patients who have residual cancer after standard neoadjuvant chemotherapy? Again, to my review, there was only one clinical trial in the literature that specifically addressed this point. It's from M.D. Anderson, a study that was begun quite some time ago in which 200 patients were randomly assigned to receive neoadjuvant chemotherapy -- excuse me, RECEIVED neoadjuvant chemotherapy -- and at the time of their surgery received additional treatment based on the pathologic response.

Those patients who had a complete pathologic response, or less than one centimeter of residual disease, went on to receive additional cycles of VACP chemotherapy. Whereas those women who had greater than one centimeter of residual disease were randomly

assigned to either ongoing similar chemotherapy with VACP or to a regimen that was considered non-cross resistant, a Vb- and anti-metabolite-based regimen. And long-term results from this study have been published by Eva Thomas in the M.D. Anderson group, and they are shown here.

What they suggest is that, in terms of relapse-free survival, the crossover to a so-called non-cross-resistant regimen did seem to improve recurrence-free survival, but the difference in overall survival was more modest. Now again, I'm not aware of other papers in this vein in the literature, but I would be grateful if people would point them out to me.

So where are we in 2007? In my assessment, the role of additional chemotherapy after standard neoadjuvant chemotherapy is entirely unclear and yet is an enormously common clinical dilemma.

The vast majority of our patients will not have a pathologic complete response in response to therapy and appear to be at greater risk for recurrence. And these women, as you've already heard today, have tumors that by definition carry some degree of resistance to chemotherapy. Many, if not all of these patients, will have had anthracycline- and alkylator- and taxane-based chemotherapy, that is to say there are no standard non-cross-resistant regimens that are immediately available, [unless patients have had less commonly administered regimens such as CMF]… (unint.) to those who continue to use MF or something like that in their regular treatment programs.

And there really are no data from the modern era to guide treatment recommendations for patients who have completed what we would think of as standard treatment program. But this is an enormously complicated clinical dilemma, and I'm sure those of you who take

care of patients like this frequently encounter consultation questions about whether to give more or not. My own personal feelings are that in the absence of any such data, that additional chemotherapy should not be routinely administered. Guidelines are surprisingly quiet on this point though the current NCCN guideline suggests that one complete what would be a standard regimen, such as anthracyclines and then taxanes, but makes no further treatment of additional therapy.

So conceptually the problem comes down to this, and again I just make use of the B-27 data because they are so familiar. Patients will either have a pathologic complete response or not. Of those 20-25 percent of women who have a pathCR, the question becomes, would more be better? And you could easily rationalize this by saying, "Yes, of course these are the women who have chemotherapy-sensitive tumors. We need to do more for them. They've proven that their tumors are exquisitely sensitive. Pounce on them. These are the women who need more treatment."

Or you could say, "Well, actually these women are doing pretty darn well already. They may be candidates for our other treatment modalities, but it's hard to think that you could substantially improve their prognosis by adding yet another type of therapeutic option."

By contrast, for those women -- the majority -- who do not have a pathCR, it's again a dilemma as to whether or not more treatment would be better. Clearly, what pushes us to even consider this is the recognition that these are women at higher risk for recurrence, and therefore there is the strong temptation to offer something more.

But as you've already heard from several commentators today, there is also the suggestion that the women who have substantial degrees of persistent tumor despite

standard chemotherapy, have cancers that are already substantially resistant and it's not clear that more would make things better.

So for this reason I believe that the post-preoperative patient -- who is everybody who gets neoadjuvant chemotherapy -- constitute a relatively unique and high-priority research population for our ongoing clinical trials.

I can tell you from consultations with many patients and colleagues here that there is tremendous heterogeneity in our current approach to these patients. It is not uncommon for us to hear clinicians topping people off with extra cycles of gemcitabine or capecitabine, or your favorite chemotherapy of the month.

But there is, as I said earlier, certainly no consensus on the best treatment approach following a delivery of standard chemotherapy, despite the higher risk of recurrence.

So I think one of the challenges here is that we need to begin to deliver on the promise and the premise of neoadjuvant therapy, which is to say that treatment can be tailored based on a dynamic response. And this is obviously an important research agenda.

As a platform for research concepts, I think the post- preoperative patient is an enormously important patient population. It provides the opportunity to look at a variety of markers of recurrence risk. These could be static markers measured either at baseline or after neoadjuvant chemotherapy, and could reflect the incidence of both systemic and local-regional recurrence.

In addition, because of the relatively high-risk nature of these patients, there is the opportunity to do serial monitoring for early detection of recurrence, perhaps in a more

efficient and more focused way than we have seen to date in the large adjuvant studies. And finally, there are opportunities for therapeutic intervention trials which could be of the "more therapy" strategy or of the novel therapy strategy.

There are a couple of efforts along this line that are going on. Dr. von Minckwitz and colleagues are conducting a trial called NaTaN, which takes women who have had preoperative therapy in the past and randomly assigns them to either observation alone or to use of the bisphosphonate zoledronate to look at important disease-related endpoints down the road. Accruement to this study continues, and as of the first of the year, they were making substantial progress in accruing patients to this trial.

I'll close by briefly mentioning some of the work we've been doing in collaboration with my colleagues at Indiana, at UCSF, and UNC as a feasibility study to look at novel therapeutics after preoperative chemotherapy, again based on the rationale that novel therapies are needed for a patient population that has residual invasive cancer despite preoperative treatment.

And we have planned a series of sequential cohorts of about 40 patients, designed to look at the feasibility and safety of therapy in this setting, and to do correlative analyses focusing on markers of angiogenesis activity and predictors of recurrence.

Our current work, which is supported by the NCI, is a pilot feasibility study of three cohorts of anti-angiogenesis-based treatment. The first cohort of women received bevacizumab for one year. The second cohort has received six months of our metronomic chemotherapy regimen with bevacizumab, and a third cohort will receive capecitabine plus bevacizumab. The preliminary data from our first cohort will be presented at ASCO. Not surprisingly, it looks like this is a feasible strategy, but our

experience also underscores the very high-risk nature of this patient population, with roughly 25-35 percent risk of recurrence in the first year alone.

And I think there has been a lot of discussion on our quarter and others about proposed trials for patients in the post-preoperative therapy setting. One concept that we are circulating, and others have contributed to as well, is the idea of using anti-VEGF or other anti-angiogenesis strategies either with or without chemotherapy or additional chemotherapy itself, in an effort to get at this question as to whether more therapy would be better and, in particular, whether novel therapeutics might improve outcomes for such patients.

So, in summary, after preoperative therapy, patients receive standard radiotherapy treatment and biologically-based adjuvant therapy with anti-estrogen or anti-HER2 treatments as appropriate, and appropriate surveillance according to standard guidelines.

Patients who've completed preoperative therapy constitute, I believe, an important population with, and I would underscore, two critical aspects -- medical needs that are both unique, and medical needs that as yet remain unmet in their oncological care.

And, finally, as I hope I've underscored, there are substantial opportunities for us to study these patients in a way that can allow them to have improvement in their cancer-related outcomes. Thanks very much.