

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
4 SESSION-1_2_HORTOBAGYI

(NOTE: “Primary” systemic therapy here refers to preoperative systemic therapy.)

DR. JEFFREY ABRAMS: Thank you. Our next speaker is Dr. Gabriel Hortobagyi, chair of the Department of Breast Medical Oncology at MD Anderson Cancer Center and the University of Texas. And Dr. Hortobagyi will talk to us about the selection of optimal candidates for neoadjuvant chemotherapy for primary breast cancer.

DR. GABRIEL HORTOBAGYI: Thank you, Jeff. Laura, Jeff, ladies and gentlemen. My thanks to the program committee for being invited to present these thoughts. My talk will be an introduction to many of the subsequent presentations. And, by force, I will give short breath to some of the information. I will also present to you a number of hypothesis-generating analyses that others will expand on after me.

So, my group presented the first paper about neoadjuvant chemotherapy probably 30 something years ago at ASCO. For us, this is the standard of care in my institution. And so if I become too much of an enthusiast, please forgive me.

As Bill [Wood] elegantly presented, preoperative -- or “neoadjuvant” -- systemic therapy has a number of potential advantages. Some of them have been clearly confirmed by clinical trials and clinical experience. Others remain in the realm of experimentation. So, certainly tumor down-staging and making a lesser surgery equally effective has been accomplished in a variety of clinical trials. And this sequence has clearly been proven equivalent to other sequences of treatment in the multi-disciplinary context.

Certainly, the ability to assess response is a very important one -- if nothing else, to stop ineffective treatment and avoid additional and certainly unnecessary toxicity; and perhaps to change to potentially more effective regimens or approaches for management of the disease. It is an outstanding experimental model in which monitoring the biological

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effects of therapy is clearly possible for prolonged periods of time. And I think we have learned much about the biology of breast cancer and the biological effects of therapy because of that.

Some of the earlier expectations in terms of the effect of early induction of systemic therapy have thus far not borne out, but, nevertheless, continue to be interesting hypothesis.

There have been a number of early randomized trials -- most of them are rather underpowered -- showing that preoperative and postoperative administration of the same regimen for the same duration of time led to equivalent survival. This was actually disappointing at that time, since all of us expected a better outcome with preoperative therapy.

B-18 confirmed this and it continues to be the largest of such comparisons. And I would like to underline what Bill [Wood] mentioned earlier -- that the lack of a survival advantage is also a lack of a survival disadvantage, therefore, pointing out the equivalence of these two approaches. Now, clearly, we have established, through multiple trials, that breast-conserving therapy is enhanced by preoperative chemotherapy and endocrine therapy, as you will hear later.

These are just a few of the larger randomized trials comparing pre-op versus post-op systemic therapy. In this case, chemotherapy -- showing in yellow the higher rate of breast-conserving therapy in the groups treated with preoperative chemotherapy. This is clearly widely accepted.

And I think the difference between the surgery first and chemotherapy first depends largely on definitions and on criteria of selections. And I think that, since the devil's in

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the details, that's where much of our discussion should focus -- not in whether this is possible or not.

So, what are optimal candidates? Which is my charge today. And my simple answer is exactly the same as Bill's: all patients who are known to be candidates for adjuvant chemotherapy -- since chemotherapy is what I'm supposed to talk about -- are candidates for pre-op chemotherapy. But as I'll show you over the next five to ten minutes, the answer is a little bit more complicated than that.

So, do all patients benefit equally from preoperative chemotherapy? And, to get to that, perhaps we should spend a couple of moments on defining "pathological complete remission", since much of our discussion over the next couple of days will use this concept. And this concept means different things to different people. And I think it's important for us to use the same language, or at least understand what language someone else is using.

So, in a very simplistic manner, and without citing all of the classifications that others will define for you later -- Fraser Symmans, for instance, will go through this tomorrow - - from the most stringent to the least stringent definitions, you could define "pathological complete remission" as the status of the surgical specimen after preoperative therapy as not showing any detectable malignant cells in the breast or lymph nodes. That could be probably the most stringent criteria.

All the way to total or near-total therapeutic effect, with some pathologically described therapeutic modifications in the residual tumor. And then there are some intermediate ones such as, invasive tumor undetectable in both the breast and the lymph nodes, or, invasive disease absent in the breast. And these intermediate ones are probably the ones most commonly used in the literature.

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Now, these are data published by one of our junior faculty. And it shows the importance -- the relative importance -- of pathological complete remission in the breast and in the regional lymph nodes. So -- this is from a series of patients who had operable breast cancer and had a fine needle aspiration of a palpable or sonographically detected lymph node in the axilla. And all of them had FNA-positive lymph nodes at the beginning. Then they received preoperative chemotherapy and had very definitive surgical resection.

The top two curves show the relapse-free and overall survival by pathological status in the breast (nodes?). And, obviously, if you have no residual disease, as shown in blue, you'll do better than if you have residual disease.

The lower two curves show the effect of having residual disease in the breast if the lymph nodes became negative. Once the lymph nodes became negative, whether you had residual disease in the breast or not, the prognosis was very similar. Now, the numbers are small, so I'm not going to tell you that it makes no difference. But, actually, the NSABP has similar data, although there is a little difference between the residual disease in the breast or not.

But the effect on lymph nodes is a major determinant of prognosis, which makes sense, because it's those nasty little cells that have the ability to travel elsewhere that determine outcome -- not the lump in the breast.

How about ductal carcinoma in situ after preoperative chemotherapy? This is also a retrospective analysis from a large group of patients treated at our institution -- about 2,200. And if you see the two curves on the top -- those with pCR with residual ductal carcinoma in situ, and those with pCR without residual ductal carcinoma in situ, do exactly the same, both in relapse-free and overall survival. So, we consider that having residual DCIS, while it might be biologically interesting, is not prognostically important.

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So, for our purposes, our favorite definition of “pathological complete remission” is, “the absence of invasive carcinoma in the breast, the absence of malignant cells in the lymph nodes, whether DCIS is present or not”.

Others will use different definitions; but I want you to pay attention to that, because some of the results are interpreted differently using different definitions.

So, many years ago -- this is by now 20 years ago -- we published on the importance of pCR as a predictor of better prognosis. Lorne Feldman published that. And then others published subsequently, confirming this concept. And I think it's pretty widely accepted that pCR is a marker of better prognosis.

However, there are a number of remaining questions about pCR. If we increase pCR rate, will survival rate increase, too? And others, especially NSABP, will address that in a little bit. Is pCR of prognostic value regardless of receptor status and other biological markers? And can patients who achieve pCR be treated with less therapy? There will be some reference to that, I think, later in the conference, although I don't think we have definite data on this.

Now, can we predict pCR, since pCR occurs several months after the diagnosis and initiation of therapy? Now, there have been multiple attempts -- individual predictive markers, mostly of a pathological nature or biochemical nature; predictive indices; functional imaging, such as PET scanning; and genetic profiling. And you will hear more about each of those later on in the conference.

To try to summarize very simplistically -- the factors described from the left side of this slide have been proposed by multiple publications to be predictive of pCR: So, pCR is inversely related to tumor size. It is directly related to higher grade. In fact, very few, if any, pCR's are achieved with low-grade tumors. It is more common in ductal as opposed

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to lobular carcinoma. It is several-fold more frequent in ER-negative than in ER-positive tumors. HER2 has a mixed history; but I'll say that it is probably predictive of a greater or higher pCR rate, as are proliferative markers and the absence of the multi-drug resistant gene.

And in this slide, I summarize for you six reports -- and there are many more -- that have looked at ductal versus lobular cancer, and the frequency of pCR after neoadjuvant or preoperative chemotherapy. And the figures in yellow show, at the bottom, that pCR is several-fold more frequent in patients with ductal than in lobular cancer -- something that is probably confounded by grade and hormone receptor status.

Hormone receptor status is summarized here. This is probably an incomplete list by now; but it shows how patients who receive preoperative chemotherapy are several-fold more likely to achieve pCR if their tumors were hormone-receptor-negative, than if their tumors were hormone-receptor-positive. And this ratio is somewhere in the range of four to six. So, it is a major difference.

Now, once you achieve a pCR, at least in our hands -- and it is, again, a retrospective analysis -- the prognostic value of pCR is the same whether you have hormone-receptor-positive or hormone-receptor-negative breast cancer. So, even though you are less likely to achieve pCR with the ER-positive disease, if you do, you are in business. And I think that's an important consideration. Again, I caution you about the small numbers on this slide.

Now, molecular subtyping by a variety of methods has also come to be considered important. If you just look at our traditional markers -- ER, PR, and HER2 -- the highest pCR rate has been observed, by several reports, in the triple-negative group and in those with ER negative, HER2 positive. All others had a much lower rate of pCR.

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If you use gene expression profiling, than the basal and HER2-like subtypes are much more likely to be associated with pCR, with higher pCR rate, than the luminal types. And these, of course, have much overlap with the previous illustration.

So, I think it is fair to say that there are no... there's no individual marker that can reliably predict response to preoperative chemotherapy in an individual patient. Although, one could hypothesize that ER-negative, high-grade tumors with high proliferative rates would be more likely to respond than patients with the opposite characteristics.

Fraser Symmans and Roman Rouzier at my institution developed a nomogram that is available for free on the Internet that helps you calculate, on the basis of easily attainable -- or obtainable -- data from the pathology report, the probability of achieving pCR. And I encourage you to use it and test it to see if it works for you. I'll be happy to share this with you later, since I can't imagine you can write it down so quickly.

Luca Gianni is probably going to show us how the OncotypeDX, as a multi-gene predictor, can predict probability of pCR.

And there are probably other multi-gene predictors that would accomplish a similar purpose.

Lajos Pusztai, who is going to speak tomorrow, has identified, by a gene-profiling method, a profile that is associated with a very high pCR rate. And this has been confirmed in a test set of patients. And we just completed accrual to a prospective randomized trial where we asked the question, whether this was just a generic predictor for chemotherapy or for a specific chemotherapy regimen? Although the analysis of that trial is not complete.

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Should we switch chemotherapy based on response to the initial regimen? There will be several presentations later in the conference that will address this. I just summarize this on this slide -- four of those trials. We started one in the early 1980s, which was unfortunately underpowered; but it was published in the JCO a couple of years ago -- showed that crossover of responders, but incomplete responders, to a non-cross-resistant regimen -- and this was before the taxane era -- results in an apparent trend in favor of the crossover regimen, as opposed to continuing with the same regimen they used preoperatively. This did not reach the levels of significance.

Smith has shown a remarkable improvement by crossover to docetaxel, something that the NSABP has not quite confirmed in B-27.

The von Minckwitz trial, GeparTrio, addresses a question specifically related to the non-responders, so it does not address the same question.

So, to conclude. Primary systemic therapy -- is it optimal for all patients? Well, as I mentioned earlier, complex problems have simple answers that are invariably wrong. So, I will have for you a somewhat more complex answer: so yes, it is optimal for candidates for systemic therapy once you're sure that the baseline characteristics are such that you would give chemotherapy in this case, or endocrine therapy. If the indication for such therapy's uncertain, I think surgery upfront is probably a wiser choice.

And, most importantly, I think, primary systemic therapy should be tailored to the biological profile of the primary tumor. And, today, we think of breast cancer as multiple, molecularly defined syndromes, and we treat these syndromes somewhat differently.

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And this is just a proposal for you -- but I think the hormone-receptor-positive tumors derive the greatest benefit from endocrine therapy. And chemotherapy may or may not be of added benefit, depending on the specific characteristics of the tumor.

HER2-amplified tumors probably benefit the most from trastuzumab, although we still have to prove that in a prospective trial; and chemotherapy is probably of secondary importance there. And so on down the line.

I think this is the way we should approach post-operative adjuvant therapy and, probably, preoperative therapy.

Most importantly, PST [preoperative systemic therapy] is not indicated when systemic therapy is not indicated; when the primary and lymph node metastases cannot be adequately measured and monitored; when the patient is not compliant with treatment -- I think it is preferable to remove that primary tumor and regional lymph nodes upfront; and when a well-oiled multi-disciplinary team is not available. I cannot over-emphasize this, because some of the differences in local-regional recurrence after primary chemotherapy I think are due to this particular factor. And we need to make sure that we talk about this.

Thank you very much for your attention. I'll be looking forward to the rest of the conference.