NCI 2007 PRE-OP THERAPY IN BREAST CANCER
34_SESSION 6_3 - COLLEONI

DR. CLIFFORD HUDIS: Our next speaker is Marco Colleoni from the European Institute of Oncology, where he is the Director of the Research Unit in Medical Senology in the Department of Medicine. He'll talk about chemotherapy response and ER, PR, and HER2, HER1 status types.

DR. MARCO COLLEONI: Thank you, Cliff. I would like to thank also the organizers of the meeting for giving me the opportunity to join this important conference. What I would like to do in the next fifteen minutes is to present some data, hopefully not already presented during the meeting, which is quite difficult to some extent, on the correlation between the response to preoperative chemotherapy and selected factors, including steroid hormone receptors and type 1 tyrosine kinase receptor, namely, HER1 and HER2.

I would like to discuss both the predictive and prognostic value of these factors, in other words, the characteristics of the tumor which might predict the magnitude of the response to a given treatment, and also the characteristics which might predict disease outcome of the patient.

Why should we focus on ER, PgR, HER1, and HER2? Well, there are some data which indicate that the patterns of treatment outcome might be related to these factors, either alone or in combination. In fact, we know that tumors that lacking ER and PgR might be particularly sensitive to preoperative chemotherapy, and that HER1 and HER2 might be linked not only with resistance to chemotherapy, but also to a worse prognosis.

And there might be also a relationship between these factors. In other words, there are subgroups of breast cancer tumors, like ER-positive and PgR-negative, which might over-express HER1 and HER2.

So, the question is, can we use these markers to tailor preoperative chemotherapy? Well, the content of this slide is well known by the audience, because several authors already spoke about this during the meeting -- it summarizes the results of the probability of achieving a pathologic complete remission according to the steroid hormone receptors. And, as you know, there is a significantly higher probability of achieving a pCR in those patients whose tumors do not express steroid hormone receptors if compared with those tumors with some expression of steroid hormone receptors.

But I would like to focus on the fact that there was a large variation in both the definition of pCR and hormone receptor positivity definition in these studies. In fact, for several authors, pCR consisted in no evidence of invasive breast cancer cells in the primary tumor. Whereas, in other studies, both in the primary tumor and in the axilla, the absence was considered as a criteria for a pathologic complete remission.

But also, the evaluation of positivity for steroid hormone receptor significantly changes between studies. These are mainly old studies, retrospective analyses. So, several studies used the biochemical assay. Others used immunohistochemistry. Others used both during the timeframe of the study. And also, several considered only ER positive as a criteria for hormone receptor positivity. Others considered ER and/or PgR positive.

And I would like to focus on the problem of the cutoff. In fact, in our experience, in our institute, we found a significant difference in the probability of achievement of pathologic complete remission only for the subgroup of tumors with no expression -- zero percent -- of both ER and PgR, if compared with the cohort of patients with some expression of steroid hormone receptor or with positive steroid hormone receptor. So, the cutoff might be relevant for the definition of a population with a true chemotherapy-responsive disease.

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This slide summarizes the results for disease-free survival… disease-free survival according to steroid hormone receptors. And, at least for early relapse, as shown in this slide, all the studies are consistent. There is a clear, poorer disease-free survival for hormone-receptor-negative tumors -- the tumors who respond very well to pre-operative chemotherapy -- if compared with the cohort of patients with hormone-receptor-positive tumors.

And we have evidence in the literature that, also for those patients with residual axillary disease at final surgery after preoperative chemotherapy, there is evidence that, in the cohort of patients with ER-negative tumors, there was a significantly poorer 5-years' relapse-free survival and 5 years' overall survival if compared with the cohorts of patients whose tumors were ER-positive.

There are quite a few data in the literature about late disease-free survival or, better… disease-free survival after prolonged observation, prolonged follow-up. And this study from the MD Anderson clearly showed that the time course of breast cancer after preoperative chemotherapy, according to steroid hormone receptors, is, to some extent, quite complex.

In fact, there was a clear, poorer disease-free survival at five years for hormone-receptor-negative tumors if compared with hormone-receptor-positive cohort. But, after about 100 months, the curves crossed. At the tenth year, there was significantly poorer disease-free survival for hormone-receptor-positive if compared with hormone-receptor-negative tumors. This study confirmed also the importance of the achievement of a pathologic complete remission, both in the cohort of hormone-receptor-positive and in the cohort of hormone-receptor-negative tumors.

In fact, the achievement of a pCR significantly correlated with prolonged disease-free survival, both in the cohort of hormone-receptor-negative and hormone-receptor-positive tumors, if compared with those patients who failed to achieve a pathologic complete remission.

The figures for overall survival after prolonged observation is in line with the results previously shown for disease-free survival. There was a poorer overall survival at five years for hormone-receptor-negative compared with hormone-receptor-positive. But, at ten years, the curves crossed, and there was a poorer overall survival for hormone-receptor-positive if compared with hormone-receptor-negative. And, once again, the achievement of pCR significantly correlated with prolonged overall survival, both for the cohort of hormone-receptor-negative and the cohort of hormone-receptor-positive disease.

Going to HER2 evaluation -- there was a large variation in the methodology used in past trials for the assessment of HER2 positivity. In fact, several studies considered only amplified tumors as -- for HER2 -- as positive. Other studies considered as positive both the 3+ through immunohistochemistry and amplified tumors. Others considered only immunohistochemistry, but 2+ or 3+. And other studies did not follow the classical criteria based on intensity, completeness, and number of positive cells in order to define HER2 positivity.

And also, the cutoff used for the definition of positivity ranged between one and ten percent [of the cells]. So, we know now, from the, for example, the ASCO[ASCO-CAP] guidelines, that this might not be the proper cutoff for the definition of a true HER2-positive population.

With all these limitations, with all these limits, I summarized, in this slide, the probability of achievement of pathologic complete remission according to HER2. And there was no clear evidence of a different probability of pCR for HER2-positive disease compared with HER2-negative disease, with the exception of the largest trial, from the MD Anderson, that showed clearly that there was a significantly higher pCR rate for HER2-positive disease if compared with HER2-negative disease.

It was of interest that, in this study, the authors evaluated both ER and HER2. And they found that the highest probability for the achievement of pCR was for the cohort with endocrine-non-responsive disease -- ER-negative, HER2-positive -- 29 percent, which decreased to 6 percent for the population with endocrine-responsive disease -- ER-positive but HER2-negative.

This is a slide that summarizes the results for disease-free survival according to HER2. At least for the larger trials, there is an evidence of a poorer disease-free survival at five years for HER2-positive disease if compared with HER2-negative disease, after preoperative chemotherapy.

I would like very briefly to present the updated results of the study that we conducted, together with the International Breast Cancer Study Group, just to show that we confirmed all the data already I presented now. In fact, we confirmed that, for the population -- about 500 patients analyzed -- for the population with ER AND PgR absent tumors, there were a significantly higher probability of pCR. We failed to observe a difference in the achievement of pCR for HER2-positive disease, if compared with HER2-negative disease, although there was a trend toward a higher probability of pCR.

But, most important, we confirmed with our updated results that, for the population with ER and PgR absent tumor, there was a significantly poorer disease-free and overall

survival at five years, if compared with tumor with some expression of steroid hormone receptor, which was confirmed at the multivariate analysis. There was also evidence of a poorer disease-free survival and overall survival for HER2-positive disease compared with HER2-negative disease; but this was not confirmed after a multivariate analysis.

And I would like to very briefly show you this exploratory biomarker analysis we performed. This is just hypothesis-generating. But just to show that the patterns of treatment outcome might be related to the combination of ER, PgR, and HER2. And, in fact, we found that the best disease-free and overall survival [was] for the subgroup with ER and PgR positive disease -- 74 percent disease-free survival, 90 percent overall survival; which decreased to 65 percent and 81 percent in the population with ER positive and PgR absent tumors, where we know there might be some expression of both HER1 and HER2.

And for the subgroup with the so-called "triple-negative" -- we know this is a very heterogeneous disease -- there was a decreased 5-year disease-free survival to 50 percent, overall survival to 69 percent. But the worst disease-free survival and overall survival, as other authors already reported, was observed for the cohort of patients with ER and PgR absent tumors and HER2-positive disease [ER-, PR-, HER2+ disease].

So, these data support the fact that, in the future, tailored treatment -- targeted treatment -- should be [explored] in select subgroups of patients.

Going through the last factor, HER1 -- very few data available in the literature for preoperative chemotherapy and HER1. As indicated in these two studies, there was no clear difference in the probability of achievement of pCR for HER1-positive disease compared with HER1-negative disease. In the first of these trials, there was a trend to a poorer overall survival for HER1-positive if compared with HER1-negative disease. But,

in this trial from the MD Anderson, there was a clear poorer disease-free survival and overall survival for HER1-positive disease if compared with HER1-negative disease.

So, in summary, for steroid hormone receptor status, negative hormone receptor status is one of the strongest predictive markers for preoperative chemotherapy. As shown before, receptor status is also prognostic, but the time course of the disease is complex, and the results change according to the time of the observation, to the duration of the follow-up.

There is controversy about the role of HER2-positive status as a predictor of response to preoperative chemotherapy. Studies indicated a worse outcome for HER2-positive disease compared with HER2-negative disease. But there is clearly a need for standardized criteria to define HER2-positive tumor in order to allow cross-study comparison.

And there are very limited data available about HER1, need for further studies. It seems not to be a consistent predictor of response, but it may have a prognostic significance.

And I would like to conclude saying that, as of today, there is very limited information on how to tailor a treatment for individual patients. There are patterns of treatment outcome very different in the selected subpopulations, with a major contrast between endocrine-responsive and endocrine-non-responsive disease. But the development of tailored research for specific niches of patients is priority for future trials. Thank you very much.