NCI 2007 PRE-OP THERAPY AND BREAST CANCER
25 SESSION 4_Talk 2_CHIA

DR. JOSEPH SPARANO: The next speaker is Stephen Chia, medical oncologist from the British Columbia Cancer Centre, and he will speak on special medical oncology issues in locally advanced breast cancer. Stephen.

DR. STEPHEN CHIA: Thank you, Drs. Albain and Sparano and the organizers of this conference. Sorry, I guess I have to bring … they are bringing my podium down.

So, in the next fifteen minutes, I've been tasked to review a few points of particular emphasis in locally advanced breast cancer: In particular, staging in locally advanced breast cancer. The inclusion of the entity of an ipsilateral supra-clavicular nodal involvements. Systemic trials of particular focus or emphasis in the locally advanced breast cancer population -- and I'll limit the review to randomized phase 3 trials. And, last -- I'll leave it to a medical oncologist -- but I'll have one slide in regards to the role of radiation in locally advanced breast cancer, and really the paucity of data.

I thought I would begin, though, with recent conclusions and recommendations of an international expert panel convened to review the neoadjuvant systemic therapy in operable and locally advanced breast cancer. And in their review and their conclusions, in the population of, specifically, locally advanced breast cancer, the primary aim was felt to be improving surgical options, with secondary aims of obtaining freedom from disease and information on tumor response.

Granted the high risk and poor prognosis of locally advanced cancer population, it's probably arguably both improving surgical options and obtaining freedom from disease are equally as important.

And if one steps back and looks at the natural history of locally advanced breast cancer, this was first described in the literature by Haagensen and Stout in 1943. In review of 1,100 patients treated with a radical mastectomy, they described five of what they called "grave signs" of locally advanced or inoperability. And in those patients that had two of these five signs, the five-year disease-free survival was only 2 percent. If they had one of these five signs, it was a 25 percent five-year disease-free survival.

In a retrospective review from the National Cancer Institute in Milan, Italy, of 450-some consecutive patients, of which three-quarters were T4 and two-thirds were N1-3, of which none of these patients received any form of adjuvant or neoadjuvant systemic therapy, median survival in this group was only 2.5 years. And, if one looks at both the inflammatory, which is the second to the bottom line, or T3, T4's with nodal involvement, the five-year disease-free survival was less than 30 percent.

So, in regard to staging for locally advanced breast cancer, in a practice guideline initiative from Ontario, Canada, they performed a systematic review of the literature. Granted, this is for post-operative Stage III breast cancer. And, in the review of the literature, their recommendations in Stage III breast cancer was for complete imaging of bones, lungs, and liver. And the detection of distant metastases in this comprehensive review was about 8 percent on a bone scan, and 2 percent with both liver ultrasound and chest x-ray.

Granted, though, the false-positive rate, as we all recognize, is particularly high, so it's not particularly specific, and one should obviously go on for further definitive -- either biopsy or further imaging; of which, one imaging modality of higher specificity is that of PET scan.

And these images are courtesy of David Mankoff. And this is looking at the PET images of a multi-centric breast lesion. But, in particular, looking at the axilla, it can help to define potentially N2 versus N1 disease. And this showing more matted nodes versus discrete nodes.

More so, in an observational study from the University of Washington, they noted, in the cohort of locally advanced breast cancer patients, up to 15-20 percent had uptake on their internal mammary nodal chain. And of these, only one of these patients was actually seen on routine imaging with a CT scan. And their conclusions was that the IM uptake was associated with non-upper-outer quadrant lesions and inflammatory breast cancer, and predicted for higher likelihood of failure and patterns of failure.

I think, further to this point, we, among others, have looked at the location of the primary breast tumor, granted again post-operative, and risk of recurrence and outcome. And in British Columbia, when we looked at close to 7,000 patients over a seven-year period, simply comparing medial- versus lateral-based lesions, despite the medial-based lesions being smaller, having less lymphatic and vascular invasion and nodal involvement, there was a worse outcome -- a five-year distant-disease-free survival difference of a hazard ratio of close to 1.5.

Now, focusing now on the ipsilateral supra-clavicular nodal involvement -- as you recognize, in 2002, the sixth (AJCC) edition had changed the staging from M1 to N3c. I think this was largely based, in part, from the experience and publication from M.D. Anderson of 70 patients with ipsilateral supra-clavicular node involvement treated with neoadjuvant anthracycline-based chemotherapy on three prospective randomized trials, followed then by local-regional treatment and then adjuvant therapy, of which they produced a 10-year disease-free survival of close to 32 percent.

We subsequently looked back at our own population-based analysis and, though smaller numbers and more variable systemic and local-regional treatment, also showed a 10- year breast-cancer-specific survival of 25 percent.

And M.D. Anderson has also shown this, when compared to both the distant metastases or Stage IIIb, it's a unique cohort with an intermediate prognosis, but a potentially curable outcome in a proportion of patients.

So, focusing now on the systemic therapy trial specific to, or with an enrichment of, locally advanced breast cancer patients. The initial and largest randomized trial was initiated by the EORTC in 1979. In this trial, with a relatively strict definition of locally advanced breast cancer, they are randomized to radiation alone, or to radiation followed by hormonal therapy, which was tamoxifen in the post-menopausal or ovarian ablation in the pre-menopausal, twelve months of classical CMF, or the combination of the two. Only in five out of these 410 patients was a mastectomy part of their treatment plan.

And when this study was updated with further follow-up and published in 1997, there were several conclusions that were put out. The best arm of the study was that of the combined chemo-hormonal treatment post-radiation, and statistically had a better distant-disease-free and overall survival than the radiation alone. Likewise, the hormonal-only treatment group performed better. But one of their conclusions was the chemotherapy arm alone did not perform better and had no difference in overall survival, though it did have a difference in distant-disease-free survival.

And round about this time, there was a number of small, randomized phase 3 trials of chemotherapy in locally advanced breast cancer -- again, most of these were adjuvant --

that failed to show an overall survival improvement. But these were all fraught with small numbers -- less than 50 patients per arm -- older regimens, and inconsistent staging.

So, I think one wants to take a leap of faith in terms of the benefits in overall survival for primary -- or neoadjuvant -- systemic therapy in locally advanced breast cancer.

This trial has already been alluded to -- the Aberdeen trial -- of which, about 40 percent were T3 to 4, and the TX N2 was only 10 percent of patients. And in the group of patients that actually benefited or had a response to the anthracycline regimen, and were subsequently randomized to the taxane -- here being docetaxel -- there was, at a p-value of 0.05, a survival benefit.

One of, perhaps, the largest trials of neoadjuvant systemic therapy in true locally advanced breast cancer population was a collaborative effort through the EORTC, the NCIC, and the SAKK group. And in this population, you note that 40 percent was T4a-c, and 45 percent was an inflammatory breast cancer population. The local-regional treatment, of note, was variable, and they were randomized to two different anthracycline regimens -- what we term the Canadian CEF, where it's oral cyclophosphamide with epirubicin, day 1 and 8 for six cycles, or dose-intensified epirubicin and cyclophosphamide delivered every two weeks with the need of Neupogen support.

And this trial, unfortunately, showed absolutely no difference in the pathological complete response, with the pCR rate in the CEF arm of 14 percent. And that of 10 percent in the EC arm. And no difference in either progression-free or overall survival. And in exploratory analysis, when they looked at the outcome in the inflammatory versus locally advanced, they showed a difference, with the inflammatory cohort showing a worse prognosis, and Dr. Swain will review that entity in detail.

Another trial, which I will not go over the results because Dr. Swain will present, is the SWOG-0012 trial of a neoadjuvant trial in locally advanced breast cancer, presented recently at ASCO, asking the question of a metronomic schedule of an anthracycline-alkylator regimen where the Adria is given weekly for 15 weeks and oral cyclophosamide, again with need of growth factor support, or that of every-three-weeks AC for five cycles, following which all patients received weekly paclitaxel.

The Anglo-Celtic Cooperative Group recently published a trial looking at anthracycline or a combination of an anthracycline-taxane regimen. In these 363 patients, this was somewhat, though not overly, enriched for the locally advanced breast cancer population. 15 percent were inflammatory, 8 percent were truly locally advanced, with the rest of them being mainly large, operable breast cancers. And six cycles of AC every three weeks, or that of Adriamycin and docetaxel every three weeks for six cycles.

And again, unfortunately, this trial was a negative trial, showing absolutely no difference in pCR rate -- roughly about 15 percent in breast and nodes -- and no difference -- this is relatively early follow-up -- in both disease-free or overall survival.

Now, one trial that may be presented later this year -- and I'd like to thank Dr. Piccart for this slide -- is the EORTC-10994 trial. An elegantly designed trial including locally advanced or large, operable breast cancer patients of close to 2,000 randomized to a non-taxane arm -- and it's really FEC or tailored FEC -- versus an arm with three cycles of induction docetaxel, followed then by three cycles of the combination of epirubicin and docetaxel.

What's elegant about this trial design is a priori, prospective biological predictive factor, based on p53, where two trucut core biopsies are performed on these patients, and a functional p53 assay is performed into yeast. And, basically -- these slides are courtesy of the P.I. of this trial, Dr. Bonnefoi -- that if the colonies turn out white, this is a wild-type p53, versus if they turn out red, as in here, it's a mutated p53.

And the a priori hypotheses is: in the wild-type p53's, there is no difference in outcome between the anthracycline and the anthracycline-taxane arm. However, in the mutated p53, this is the group to benefit from the anthracycline-taxane. Now, with a 15-percent absolute difference, they're predicting, or projecting, for the anthracycline-taxane arm.

Now, that is a brief, but obviously a brief review of the trials specifically in systemic therapy for locally advanced breast cancer.

And if you think those are relatively few and far in between, there's a further even lack of trials regarding radiation in the role of locally advanced breast cancer. This will be reviewed by Dr. Buchholz tomorrow morning. He won't go over data for Stage III breast cancer, but keep in mind this is FOLLOWING (neo?)adjuvant systemic therapy.

And I think in the day-to-day clinic, there are a few questions that do need to be addressed that we come across routinely, and that is timing -- radiation prior to or following surgery?

Fields. Does one include the IMC or not? And is there a cohort of patients that can be spared at least some fields of local-regional radiation?

So, in conclusion, I think complete staging in locally advanced breast cancer is important. And I would say that PET scanning may -- I'm not saying it should be part of the standard work-up -- but may be useful in certain patients if, in discussion with your multi-disciplinary team, it may change your local-regional treatment.

The entity of isolated supra-clavicular nodal involvement and inflammatory have different outcomes in locally advanced, and one should either stratify them or do separate trials in them, and those are being done, at least in the inflammatory cohort.

I would say there's definitely a limited number of trials, and one big conclusion would be more trials need to be done specifically in locally advanced breast cancer.

But the trials that have been done, and I'll italicize, APPEAR to show that the addition of a taxane improves outcome, and that dose-dense (correction: dose-intensified) -- at least based on this one large trial -- anthracycline regimen does not improve outcome, but maybe perhaps a metronomic schedule may. And the sequential versus concurrent improves outcome.

But the caveats are, these are based on single trials and really needs to be replicated and further explored in other large, randomized trials.

In addition, the role of radiation following neoadjuvant chemotherapy really needs to be explored and studied, as there is really no trials in this area. Thank you for your attention.