Discussion and Summary

Kennedy: Why do we talk about node-negative patients rather than use the international staging systems of stage I and stage II?

Wolmark: We have never been enamoured with the TNM classification scheme. When we analysed the efficacy of adjuvant therapy in patients with histologically negative nodes, it appeared that the efficacy of adjuvant therapy (either in B13 or B14) was not related to tumour size, and even the smallest of tumours demonstrated a benefit from adjuvant therapy. Thus, in our experience, size is not an important consideration for therapy.

Plotkin: In a number of slides describing survival differences after adjuvant therapy I am struck by the fact that when benefit is shown, the curves separate for the first 5-6 years and then they remain parallel. Would the panel discuss the significance of that observation?

Peto: We have really good data for only up to about 5 years although there are plans for another cycle of the overview. No one trial will be big enough to answer reliably whether these curves stay apart, diverge or converge, and it is only by an overview of all of the trials that we shall find out what the 5-year differences mean at 10 years.

Plotkin: Has anybody seen these curves come together in studies with tamoxifen?

Wolmark: I do not think they come together. In the NSABP data, survival lags behind disease-free survival, and then the curves separate later on. This is a point for examination.

Hammond: Regarding the duration of use of tamoxifen, surely the 2-year group and the 3-year group should be compared only after the third year, because there might be a static effect from this extra year of tamoxifen rather than prolonged effects.

Wolmark: When we do that, the differences are even bigger because the curves do not separate until the third year. For the first 3 years of therapy, the two curves are superimposable, and it is only after the third year that the disease-free survival curves (and a little later the actual survival curves) become different. If we started the analysis for the additional year of tamoxifen at 3 years, the results would have been even more significant than was presented.

Fletcher: It is possible that some patients benefit from therapy while others are made worse. When they are all grouped together, we cannot distinguish the two groups except, for instance, that premenopausal patients do not do as well as postmenopausal patients.

Wolmark: The survival disadvantage was seen in only one instance, and that was the NSAB protocol B-09 for premenopausal patients, particularly those who were progesterone-receptor negative. In that group, patients do less well if they received added tamoxifen compared with those receiving chemotherapy alone, suggesting that there may be some negative interaction between the tamoxifen and L-phenylalanine mustard (LPAM) and 5-fluorouracil (5-FU). This was explained on the basis of tamoxifen interfering with efflux and influx of LPAM specifically, and whether this occurs also with other chemotherapeutic agents has not been demonstrated.

probably does not, but we are addressing that issue in protocol 16 by using Adriamycin and cyclophosphamide with or without tamoxifen. There are sufficient questions to re-open the whole issue of tamoxifen use in premenopausal patients, and for that reason I think the ECOG study is particularly important in that it explores the effect and duration of tamoxifen in premenopausal patients. Mouridsen: I think we ought to stress that for a number of reasons, the results of these subgroup analyses should not be taken as recommendations to treat or not treat specific subgroups of patients. They should be taken as hypothetical questions to be answered in future prospective trials.

Carbone: Now that some trials in Europe have suggested benefit in node-negative patients from either tamoxifen or chemotherapy, what do we do with those patients who were operated on previously? Would it make a difference if we delayed treatment 1 year, 2 years or even 3 years in these patients?

Mouridsen: To postpone treatment for 3 years would increase the likelihood of over-treatment. After 3 years, perhaps one quarter or half of those who would experience recurrence would have had it already. So the prognosis of the patients who survive at 3 years is significantly better than it is immediately after primary treatment.

Parhboo: Dr. Mouridsen is clearly encouraging us to take part in clinical trials but the vast majority of patients with breast cancer are treated outside trials and do not have receptor measurements carried out. What is advised for node-negative patients who do not have receptor analysis? This has tremendous implications for health service budgets, particularly because patients are now demanding tamoxifen.

Peto: There is no evidence that the receptor assays done in the trials have picked out a group of wholly non-responsive women. Until we have an assay that can pick our wholly non-responsive women, one might want to treat all cases. If the assay is not conveniently available, I do not think that this is an obstacle to treatment, and for example, the British Consensus Development Conference did not require treated patients to be ER-positive.

Biggs: There is confusion about the effect on response of age and menopausal status. I wonder if there are indeed no qualitative differences in the response to tamoxifen if we consider real premenopausal and real postmenopausal patients. The differentiation between patients aged > 50 years and < 50 years is in these circumstances, artificial.

Wolmark: We found age to be as important a discriminant as any, including menopausal status. Age and decades have been sensitive indicators relative to tamoxifen response, and we shall continue to use those in preference to menopausal status.

Peto: I believe that response of advanced disease to tamoxifen is seen in a number of premenopausal patients as well as in postmenopausal patients. The idea that it is ineffective in premenopausal women is not at all well established.

Wolmark: I agree. Our data show excellent response with tamoxifen in patients who are premenopausal and node negative, where intuitively one would have thought that this group would not respond. From a conceptual standpoint, this forces us to reconsider a great many concepts that we had accepted, perhaps erroneously, relative to the efficacy of tamoxifen.
Donnegan: Dr. Mouridsen brought up the point that we may not be using the correct discriminants for choosing women for either chemotherapy or for tamoxifen, and that there are other parameters of a more biological nature that perhaps should be used. Should future trials continue to be based on ER status, menopausal status or age, or should we now be planning to use more biologic discriminants? If so, which ones are most promising?
Peto: Whatever is used, do not exclude them from randomisation!
Mouridsen: Ideally, we should use discriminants that are known to be related to efficacy of the therapy.
Carbone: To sum up. We heard from Dr. Peto that one should be very cautious about subgroup analysis and certainly that the trends looked at should be quantitative rather than qualitative. Biologically this makes sense. Based on his data, one can suggest that there is a positive benefit from adjuvant therapy in both pre- and postmenopausal patients.
Dr. Wolmark has suggested, in trying to answer the question about the duration of tamoxifen treatment, that 3 years is certainly better than 2, and the question has been raised about 5 years or longer. We need to know however, what are the long-term hazards of giving this treatment to premenopausal patients for 5, 10, 15 or 20 years, or even to postmenopausal patients. In younger women as well, there may be some hazards associated with pregnancies.
Dr. Mouridsen addressed the question of whom to treat? We started off in 1970 treating patients who were ‘high risk’ but now it has been suggested that all patients should be treated with adjuvant therapy. Dr. Mouridsen has correctly suggested that we are benefiting only a small percentage of these patients and that favours a relatively non-toxic treatment like tamoxifen. No one talked about the duration of chemotherapy, but it does look as if benefit can be achieved with as little as 6 months of treatment.
Finally, all of us know that some patients with desperate clinical prognostic features such as 10-20 positive nodes, do well, while some with small tumours which are ER-positive, do poorly. When we come down to individual patients, we talk about probabilities, but an individual patient is either cured or not cured, she cannot be 20 or 80% cured. So ultimately, we shall come to the point where we need to indentify in individual patients, what the risk is and what specific therapies need to be given.
The future will hopefully be using growth factor controls and more specific ways of controlling breast cancer. We need to look ahead and develop not just adjuvant therapy, but a strategy that affects the whole disease.