Symposia

489

Pharmaco-genomics in breast cancer

Abstract not received.

490

The problem of metastases in breast cancer

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Despite apparently successful treatment for breast cancer around 50% of node positive and 30% of node negative patients will relapse. The principal problem is distant metastasis which accounts for the mortality in this disease.

Local recurrence only has a small adverse effect on mortality rates (Oxford Overview 2000).

Several studies have shown the presence of circulating tumour cells in both blood and bone marrow. RT-PCR and other molecular biology techniques may detect such micro metastases when tumour associated markers such as CK19, MUC1 and maspin are used as the target molecules. Using these techniques up to a 33% of patients will have detectable circulating tumour cells. The long term prognostic significance of such cells are still unclear although some groups have demonstrated reduced survival in patients with circulating tumour cells in bone marrow aspirates. However highly sensitive detection techniques such as RT-PCR can produce false results.

There is much current interest in micro metastases in lymph nodes since the emergence of sentinel node biopsy. Serial sections and the use of cytokeratin immuno histochemical techniques consistently upstage conventional H & E studies by 10-20%. Once again the prognostic value of such upstaging is yet to be determined. However there is little doubt that these new techniques for detection of micro metastases will assume greater prominence in the future.

491

Intensity modulated radiation therapy (IMRT) in breast cancer

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Modulating the intensity of small segments of the radiation beam independently in an appropriate manner will improve the patients dose distribution. The introduction of multileaf collimators has advanced the implementation of IMRT into daily clinical practice by providing an efficient means of modifying the beam aperture. The collimator leaves can move during irradiation and modulate the radiation dose to the target volume. With IMRT, higher radiation doses can be delivered to a small volume resulting in a higher tumor control rate. It also provides a method of sparing critical normal tissues such as heart and lungs. For breast cancer, an IMRT approach is under investigation as a method of delivering a higher radiation dose to the tumor bed (as part of the breast-conserving therapy) and avoiding late radiation sequellae (in patients receiving post-mastectomy radiotherapy).

A recent EORTC trial that included 5569 patients, demonstrated a significant reduction in the local recurrence rate (~50%) when an additional 16 Gy radiation dose to the tumor bed in patients receiving breast-conserving therapy. The largest absolute gain in local control was observed in young women. To avoid side effects like fibrosis and poor cosmetic outcome, one should limit the irradiated volume to the original tumor bed. IMRT makes this possible by its precise delivery of the higher radiation dose to the original tumor bed.

Meta-analyses from previous trials on the value of post-mastectomy radiotherapy have demonstrated that the gain in survival obtained by better local control is counterbalanced by an increase of non-breast cancer related deaths. The causes of death are mostly vascular due to older radiation techniques. Recently, a number of trials have confirmed the value of post-mastectomy radiotherapy by demonstrating improved local control and survival. Avoiding sequellae is important for patients whose lungs and heart, as a consequence of their anatomy, will be excessively irradiated. IMRT class solutions are now being developed to reduce the irradiated volume of the lungs and heart. These techniques can also be applied for left sided breast cancer patients receiving breast conservation treatment, where conventional irradiation inadequately spares the heart. The implementation of IMRT in the clinic will further optimize radiation treatment for breast cancer patients, aiming towards improving the cure rate and minimization of its side effects.

492

Changing concepts in hormonal therapy

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Hormonal therapy remains a mainstay in the treatment of metastatic breast cancer and in the adjuvant setting. Specific approaches however have changed in both pre and postmenopausal women.

In the postmenopausal setting the non-steroidal aromatase inhibitors (AI) anastrozole and letrozole are now well established as important and perhaps preferred alternatives, not only in second line, but also in the first line setting for metastatic disease. While data from a small randomized Phase II trial of the steroidal AI exemestane suggest equivalence or superiority to tamoxifen, additional data is required. There is however excellent phase II data suggesting clinical activity of exemestane in women whose disease has progressed following therapy with other AI's. We await with great interest the early results of trials which have compared an anastrozole to tamoxifen and to the combination in the adjuvant setting. The results of this and other studies of AI's in the adjuvant setting will set practice patterns for the coming decades. The new pure antiestrogen Faslodex has already been shown to be at least equivalent and perhaps better in comparison to the AI's anastrozole in women whose tumours have progressed following tamoxifen. Further results with Faslodex in the metastatic setting are awaited with great interest and will shape plans for trials of Faslodex in adjuvant therapy.

In premenopausal women the use of ovarian ablation has been resurrected by the advent of the LHRH analogues. Several small trials of these drugs in the metastatic setting in combination with tamoxifen have suggested superiority for the combination. In the adjuvant setting LHRH analogues alone or in combination with tamoxifen, and compared to or added to CMF type chemotherapies have established ovarian ablation as an alternative to CMF type chemotherapy in premenopausal women with estrogen receptor positive tumours. The role of ovarian ablation added to CMF and other more effective chemotherapy regimens in this setting is still being explored.

493

The Meta-Analysis of Adjuvant Breast Cancer Treatment (Strengths/Limitations/Practical Use)

Peter M. Ravdin. *University of Texas Health Sciences Center San Antonio, USA*

Every 5 years the Early Breast Cancer Trialists' Collaborative Group analysis of the effectiveness of adjuvant therapy of breast cancer is initially presented and discussed at Oxford. An effort is made (which is remarkably successful) to obtain the individual patient data from all randomized clinical trials of the treatment of early breast cancer. There are strengths and limitations to this approach. Combining information from multiple trials increases the statistical power to see the often modest effects of systemic adjuvant therapy and to investigate the effectiveness of adjuvant therapy in patient subsets. The weakness of this approach is that it represents a grand averaging of information and may obscure important differences between regimens