Symposia

489

Pharmaco-genomics in breast cancer

Abstract not received.

490

The problem of metastases in breast cancer

R.E. Mansel. *UWCM, Cardiff*

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

H. Bartelink. *The Netherlands Cancer Institute, Radiotherapy Department, Amsterdam, The Netherlands*

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

Kathleen I. Pritchard. *Toronto-Sunnybrook Regional Cancer Centre, University of Toronto, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5, Canada*

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

and underestimate the effectiveness that may be afforded by the better regimens.

Even given these caveats, the Oxford meta-analysis is our best look into 2 decades of information from randomized trials of adjuvant therapy. The results presented at the September 2000 overview of the effectiveness of adjuvant therapy (tamoxifen and/or polychemotherapy) did not differ substantially from those presented in 1995 and published in 1998. They suggest that all major subsets of patients can expect a reduction in risk of recurrence and breast cancer related death from adjuvant therapy.

Approximate Proportional Risk Reductions For Mortality

Age		Tamoxifen	Chemo	Combined*
<50	ER+	25%	25%	45%
	ER−	0%	35%	−
>50	ER+	25%	10%	35%
	ER−	0%	20%	−

* Inferred given apparent independence of effects.

The Overview suggests that not all poly chemotherapy regimens are equivalent and in particular regimens that include an anthracycline seem better (with about a 16% additional proportional risk reduction) than regimens that do not. The reductions are modest, but important, particularly for women with moderate to high risk of recurrence. Of course for women with a low risk of recurrence and death the risks associated with adjuvant therapy may outweigh the benefit. More detailed information from the Oxford 2000 analyses will be presented, as well as a discussion of some probable important differences in different classes of adjuvant polychemotherapy regimens, and how this information might be used by the clinician.

494

Colon cancer

Buyse Marc. *International Institute for Drug Development, Brussels, Belgium*

Background: Treatment of advanced colorectal cancer has made substantial progress recently. However, improvements in response rates have not always translated into significant survival benefits, which has raised doubts about the usefulness of tumour response as a clinical endpoint.

Methods: Meta-analyses were performed on individual data from 3,791 patients entered in 25 randomised trials comparing first line treatment with bolus intravenous 5-fluorouracil (5FU) ("bolus FU") with experimental treatments ("experimental FU") consisting of 5FU + leucovorin, 5FU + methotrexate, 5FU continuous infusion, or hepatic arterial infusion of 5-fluoro-2'deoxyuridine (FUDR). Two further meta-analyses comparing bolus FU +/− leucovorin to the same + a-interferon were used to validate the results on individual data from 3,254 patients.

Results: Compared with bolus FU, experimental FU led to significantly higher tumour response rates (odds ratio = 0.48, P < 0.001) and longer survival (hazard ratio = 0.90, P = 0.003). The survival benefits could be explained by the higher tumour response rates. However, a treatment that reduced the odds of failure to respond by 50% would be expected to reduce the odds of death by only 6%. In addition, less than half of the variability of the survival benefits in the 25 trials could be explained by the variability of the response benefits in these trials.

Conclusions: Increases in tumour response rate translate into small increases in survival for patients with advanced colorectal cancer. However, in the context of individual trials, knowledge of a treatment's benefit upon tumour response does not allow an accurate prediction of its ultimate benefit upon survival.

495

Locally advanced head and neck cancer: meta-analysis of updated individual data

J.P. Pignon[1], B. Baujat[1], C. Hill[1], J. Bourhis[2]. *MACHNC Collaborative Group; [1] Institut Gustave Roussy, Dept of Biostatistics and Epidemiology, Villejuif, France; [2] Institut Gustave Roussy, Dpt of Radiation Oncology, Villejuif, France*

The MACH-NC study (Lancet 2000; 355:949) is based on the individual updated data collected on 10 741 patients in 63 randomized trials comparing loco-regional treatment to the same loco-regional treatment + chemotherapy (CT).

The relative risk of death (RR) with CT as compared to without was 0.90 (95% Confidence Interval (CI): 0.85-0.94). There was a significant heterogeneity between trials (p<0.0001). Using a graphical method, 5 trials (811 patients) were identified as major contributors to this heterogeneity. A sensitivity analysis showed that after exclusion of these 5 trials, the heterogeneity was no more significant (p=0.14) and the RR was practically unchanged (RR=0.91, 0.87-0.96).

The results of MACH-NC were statistically different according to the timing of CT (p=0.005). The five trials with outlying results included four trials with CT concomitant to radiotherapy and one trial with adjuvant CT. After exclusion of these 5 trials, the effect of CT timing was no longer significant (p=0.34), the RR for the adjuvant subgroup of trials decreased from 0.98 (CI=0.85-1.12) to 0.91 (0.78-1.06), the RR for the concomitant subgroup increased from 0.81 (CI=0.76-0.88) to 0.88 (CI=0.81-0.95) and the RR for neoadjuvant subgroup was unchanged (RR=0.95, CI=0.88-1.01).

Lastly, in the neoadjuvant group, there was a significant benefit of platin + 5-FU trials (HR=0.88, 0.79-0.97), significantly different (p=0.05) from the effect of other neoadjuvant CT (HR=1.01, 0.92-1.10).

In summary, the small benefit of chemotherapy observed in locally advanced head and neck cancer is robust to exclusion of outlying trial results. The results concerning the benefits of chemotherapy by timing are not. The planned update of MACH-NC which will add more than 25 trials and 8 000 patients will clarify this issue since most of these trials study chemotherapy given concomitantly with radiotherapy.

496

Overview of rectal cancer trials

Richard Gray, Robert Hills, Joanna Marro, Rebecca Stowe. *University of Birmingham Clinical Trials Unit, Birmingham B15 2RR on behalf of the Colorectal Cancer Collaborative Group.*

Chemotherapy (CT) and radiotherapy (RT) have the potential to improve survival in rectal cancer. To help define the size of benefit achievable for different types of patient, and the optimal CT and RT regimens, a meta-analysis of all randomised trials of CT or RT, in colon and rectal cancer, was undertaken. Individual patient data were sought from all relevant studies starting before 1995. If individual patient data could not be obtained, information was abstracted from published data as far as possible. Individual patient data were available on 6633 patients in 14 trials of preoperative RT, and on 2157 patients in 8 trials of post-operative RT. Preoperative RT reduced the annual risk of local recurrence by 44% SD6 (p<0.00001) and postoperative RT reduced it by 33% SD11 (p=0.002). Overall survival was only marginally better among patients allocated RT but preoperative RT, at biological equivalent doses over 30Gy, reduced the risk of death from rectal cancer (22% SD5, p=0.00002) and, to a lesser extent, death from all causes (56.5% vs 58.9% dead; p=0.04). Data were available from 50 CT studies, involving 18,000 patients. Almost all CT regimens tested involved 5-fluorouracil (5-FU), with or without other drugs. Short bolus CT regimens appeared ineffective. Short portal vein infusional regimens may improve survival marginally. The largest benefits were seen in studies of prolonged 5-FU biomodulated by folinic acid (29%SD9;p=0.0007) or by levamisole (25%SD7;p=0.0003) but these studies included almost exclusively colon cancer patients. The mortality reductions in studies testing unmodulated 5-FU regimens were smaller (6%SD4;p=0.11) but appeared at least as large for rectal as colon cancer. There remain unanswered question, therefore, about CT for rectal cancer, in particular for node-negative patients.

497

Radiation carcinogenesis

Elaine Ron. *National Cancer Institute, Bethesda, MD, USA*

Although cancer of the thyroid gland is relatively rare, it is by far, the most common malignancy of the endocrine system. External radiation is the only well established cause of thyroid cancer. Extensive information from studies of people exposed to medical irradiation, as well as the atomic bombings in Hiroshima and Nagasaki clearly demonstrates that the thyroid gland is highly sensitive to the carcinogenic effects of exposure to x- and γ radiation during childhood. Among people less than 20 years old at the time of exposure, the risk of developing thyroid cancer increases significantly with increasing radiation dose and decreasing age at exposure. The trend in risk with dose is consistent with linearity. Following radiation exposure, the elevated risk of thyroid cancer appears to continue throughout life, but there is some indication that the risk may be highest 15 to 19 years after exposure. Data regarding adult exposure are limited, but there is little evidence of an association between exposure after age 20 years and thyroid cancer risk. Investigations of patients examined or treated with radioactive iodine do not demonstrate a link between ^{131}I and the risk of thyroid cancer. However, the patients evaluated were almost all adults and, therefore, these