the distinct tumor entity ALK-positive ALCL. The fusion gene represents a tumor marker that can be exploited for diagnostic purposes and a tool to study bone marrow (BM) and peripheral blood (PB) minimal residual disease (MRD). Gene expression profile and proteomic analysis have recently been used to study ALCL.
We analyzed NPM-ALK transcript expression in tumor biopsies from children enrolled in the AIEOP LNH97 trial for ALCL and found that more than 90% of the cases were positive. BM aspirate was also studied for tumor dissemination by RT-PCR. The prevalence of minimal BM disease at diagnosis was 60%. When analyzed by real-time PCR, NPM-ALK expression levels showed a wide variability, but NPM-ALK copy number was generally higher in PB compared to BM.
In our study, minimal BM infiltration by tumor cells at diagnosis was a negative prognostic factor as children with positive BM fared significantly worse that the negative counterpart. In addition, we found that the majority of the patients had serum anti-ALK antibodies at diagnosis and that initial levels, as well as titer decrements, varied significantly among patients.
Recently, the differential gene expression profile of a series of ALCL was published. The results of such a study confirmed that differences exist at the transcriptome level between ALK-positive and ALK-negative ALCL and that distinct signatures may be associated with different histological subtypes. Gene expression profiles and proteomic analysis of ALCL cells have identified several tumor associated markers that could possibly be exploited both for diagnosis and for therapeutic intervention.
We have also studied the fate of the fusion protein NPM-ALK and its interactions with the heat shock proteins. Our data support a role of hsp70 and hsp90 in folding, activity and degradation of NPM-ALK.
Recent advances in the biology of ALCL will improve our understanding of ALCL tumorigenesis, will allow us to determine the role of MRD and will be of great relevance to define new therapeutic targets in this disease.

183 INVITED

Molecular diagnosis and prognosis in rhabdomyosarcoma

S. Gallego. *Spain*

Abstract not received.

Thursday, 27 September 2007

Symposium (Thu, 27 Sep, 09:00−11:00)
Advances in new drugs for breast cancer

184 INVITED

The pros and cons of signal transduction inhibitors in breast cancer

J. Baselga. *Spain*

Abstract not received.

185 INVITED

Inhibiting angiogenesis – a new weapon in the therapeutic armamentarium

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Over the last three decades substantial laboratory and clinical evidence has accumulated to support the central role of angiogenesis in breast cancer progression. Multiple angiogenic factors are commonly expressed by invasive human breast cancers with the 121-amino acid isoform of vascular endothelial growth factor (VEGF) predominating. Bevacizumab (Avastin™, Genentech, South San Francisco) is a humanized monoclonal antibody directed against all isoforms of VEGF-A. A phase I/II study testing three different doses of bevacizumab monotherapy (3, 10, or 20 mg/kg every two weeks) in 75 patients with previously treated MBC reported a 9.3% objective response rate with 17% of patients responding or stable at 22 weeks. In a phase III trial the addition of bevacizumab to capecitabine in patients previously treated with anthracyclines and taxanes significantly increased response rate (9.1% vs. 19.8%; $p = 0.001$) but not progression free (4.17 vs. 4.86 mo; HR = 0.98) or overall survival (15.1 vs. 14.5 mo). As VEGF inhibitors such as bevacizumab are likely to be more effective in patients with less heavily pretreated disease, E2100 compared paclitaxel monotherapy to paclitaxel plus bevacizumab as initial chemotherapy for patients with MBC. Combination therapy significantly increased response rates in all patients (35.8% vs. 20.9%; $p < 0.0001$) and in the subset of patients with measurable disease (47.2% vs. 25.2%; $p < 0.0001$). Paclitaxel + bevacizumab significantly prolongs PFS (11.3 vs. 6.0 mo; HR = 0.60, $p < 0.0001$). Grade 3/4 hypertension (15% vs. 0%; $p < 0.0001$), proteinuria (3.5% vs. 0%; $p = 0.0002$), headache (2% vs. 0%; $p = 0.009$) and cerebrovascular ischemia (2% vs. 0%; $p = 0.009$) were more frequent in patients receiving paclitaxel + bevacizumab. Additional studies will determine the impact of adding bevacizumab to other treatment regimens. Angiogenesis inhibitors significantly curtail primary tumor growth and establishment of metastases in several pre-clinical minimal disease models; overt shrinkage of large, well established tumors is less common. As tumors progress, increasing numbers of pro-angiogenic peptides are produced making resistance to any single anti-angiogenic agent more likely. As such, the most successful clinical application of angiogenesis inhibitors is likely to be in patients with micrometastatic disease that is in the adjuvant setting. Clinical trials evaluating bevacizumab in the adjuvant setting have begun.

186 INVITED

Synthetic lethal approaches as potential therapies for tumours deficient in DNA repair pathways

A. Ashworth. *The Institute of Cancer Research, Breakthrough Breast Cancer Research Centre, London, United Kingdom*

About one in nine women in the Western world develop cancer of the breast and at least 5% of these cases are thought to result from a hereditary predisposition to the disease. Two breast cancer susceptibility (BRCA) genes have been identified and mutations in these genes account for most families with four or more cases of breast cancer diagnosed before the age of 60. Women who inherit loss-of-function mutations in either of these genes have an up to 85% risk of breast cancer by age 70. As well as breast cancer, carriers of mutations in BRCA1 and BRCA2 are at elevated risk of cancer of the ovary, prostate and pancreas. The genes are thought to be tumour suppressor genes as the wild-type allele of the gene is observed to be lost in tumours of heterozygous carriers. Both BRCA1 and BRCA2 have significant roles in the maintenance of genome integrity via roles in the repair of DNA damage via homologous recombination. The specific DNA repair defect in BRCA-mutant cells provides opportunities for novel therapeutic approaches based on selective inhibition of functionally interacting repair pathways. These approaches may also be applicable to a wider range of sporadic cancers.

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187 INVITED

Challenges and opportunities in the intergration of new and old treatments

K.S. Albain. *USA*

Abstract not received.

Symposium (Thu, 27 Sep, 09:00−11:00)
Controversies in the local management of breast cancer

188 INVITED

Lessons and questions from the overview

T. Whelan. *Hamilton Regional Cancer Center, Dep. of Radiation Oncology, Hamilton Ontario, Canada*

Randomized trials of adjuvant treatment for early breast cancer may be too small to reliably detect important differences in long-term survival and recurrence. The 2000 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview (Lancet 2005; 36:2087) considered randomized

trials of local treatments in early breast cancer beginning before 1995. Information was available for 78 randomized trials involving 42,000 women (23,500 in trials of radiotherapy (RT) vs. no RT; 9,300 in trials of more vs. less surgery; and 9,300 women in 17 trials of more surgery vs. RT).
Major findings from the update were: (1) breast cancer mortality was reduced with RT following breast-conserving surgery [hazard ratio 0.83, 95% CI 0.75−0.91 (p = 0.0002)]. This effect was seen for node-negative and node-positive disease and paralleled the substantial reduction in local recurrence seen at 5 years; (2) a reduction in breast cancer mortality was also seen post-mastectomy in node positive patients (p = 0.002). No effect was seen for node-negative disease; (3) an important relationship between local control and the impact on breast cancer mortality was observed. In most trials of RT, the impact on local recurrence was seen rapidly and substantially by 5 years. Little effect in breast cancer mortality was observed in the first 2−3 years, but a definite effect was seen at 10 years and was maximally at 15 years. Among the 25,000 women in whom there was a reduction in local recurrence at 5 years of >10%, there was an absolute reduction in breast cancer mortality at 15 years of approximately 5%; and (4) the use of radiotherapy was associated with an increased incidence of contralateral breast cancer (rate ratio (RR) = 1.18, p = 0.002), lung cancer (RR = 1.61, p = 0.0007), leukemia and soft tissue sarcoma. There was an associated increase in non-breast cancer deaths mainly involving heart disease (RR = 1.25, p = 0.00003).
Since this update the 2005/06 cycle of the EBCTCG has commenced including additional trials started in 1995–2000 with extended follow-up up to 2005. A preview of these findings and implications for clinical practice and research will be presented.

189 INVITED

Does everyone need breast radiotherapy?

J. Yarnold. *The Institute of Cancer Research, Academic Unit of Radiotherapy, Sutton, United Kingdom*

The risk of local tumour relapse has fallen to such low levels for most patients after breast conservation surgery, systemic therapies and radiotherapy for early breast cancer that it prompts reassessment of guidelines that recommend breast radiotherapy in all cases. Trials randomising to radiotherapy versus no radiotherapy primarily test treatment effect, but they also offer valuable prospective data on the consequences of observation (no radiotherapy) in well-characterised populations. These typically include women aged over 50 years with completely excised oestrogen receptor (ER) positive, node negative tumours less than 20 mm in microscopic diameter. Recent results have been interpreted as evidence that radiotherapy can be safely withheld in defined subgroups, but these judgements seem premature based, as they are, on trials with less than 5−10 years follow up. Nevertheless, several factors are likely to be driving local relapse risk down independent of radiotherapy, including patient selection for breast conservation and more careful attention to surgical excision margins. In addition, advances in adjuvant systemic therapy are having a significant impact. The 2005 update of adjuvant systemic therapy by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) confirms that 5 years tamoxifen or several months of polychemotherapy reduce the annual hazards of local relapse to a similar extent as distant metastases. This amounts to a 50% reduction in local relapse risk after 5 years tamoxifen in ER positive tumours. After cytotoxic therapy, the magnitude of local effect depends on drug regimen and ER status, but is substantial in ER negative tumours. Preliminary data from trials testing adjuvant aromatase inhibitors report a reduction in local relapse risk of around 30% compared to tamoxifen alone. The combined effects of tamoxifen and aromatase inhibitor are, therefore, comparable to the benefits of radiation (hazard ratio = 0.3). The effects of trastuzumab in patients over-expressing the HER2 protein are also impressive, reducing local relapse risk by around 50%. In conclusion, while it is not currently possible to confidently identify subgroups with <10% risk of local relapse at 10 years after surgery and appropriate systemic therapies alone, it is likely that selective avoidance of breast radiotherapy in defined subgroups will be possible in the next 5 years or so. The selection process is likely to take account of encouraging evidence that biological markers help to reliably define low risk subgroups.

190 INVITED

Partial breast irradiation – a valid option?

A. Fourquet. *Institut Curie, Dept. de Radiothérapie, Paris, France*

Partial breast irradiation (PBI) is a new modality of radiotherapy, delivering radiation solely to the surgical area of excision in the setting of breast conservation of small breast cancer.
PBI was originally designed to allow breast conservation to patients with small tumors, who, because whole-breast radiotherapy (WBR) over several weeks could not be carried out in some areas due to distance to radiotherapy centers, costs, or long waiting lists, were treated with mastectomy. The first reports of PBI were of series of highly selected patients treated with conventional low-dose rate brachytherapy using Iridium 192, implanted through plastic catheters in the surgical site area, treating a wide volume, with doses around 50 Gy over 5 to 6 days. Reports from these experiences suggested that 5-year local control rates were similar to those obtained with WBR.
More recently, new techniques were introduced and are still under evaluation, aiming at targetting smaller treatment volumes, and at reducing the treatment time with accelerated irradiation (APBI). These techniques include: high dose rate brachytherapy, delivered through ambulatory care, or external beam photon radiotherapy. In both instances, a 50 Gy or more "biologically equivalent" dose is usually delivered in 10 or more fractions, twice daily with at least 6 hours interval, over 5 days. Another technique uses intraoperative radiotherapy with low-energy photons or electrons, delivering a single dose of radiation in the surgical bed immediately follwing excision. Results from these various techniques are reported with short follow-up in selected patients. Several prospective phase III randomised trials are ongoing in North America and Europe.
Obvious advantages of these techniques are practical: the reduction of overall treatment time makes it possible for patients to undergo treatments which otherwise they would be able to afford daily over several weeks, because of physical incapacity, distance to radiotherapy centers, professionnal constraints, or in some countries, cost of treatment. Treating the site of excision only with a predetermined margin would limit irradiation of organs at risk, such as the heart, lungs, or contralateral breast. Finally, the short overall treatment time would allow an earlier delivery of irradiation in patients who receive adjuvant chemotherapy.
However, this new technique raises many issues that need to be solved before it can be recommended for routine practice. Among them are the following:

- What will be the consequences of not treating the whole-breast, as achieved by mastectomy or WBR, as has always been the basis of the locoregional treatment of breast cancer? The rationale of this new paradigm relied on the observation that the majority of breast recurreces occurred within the area of the primary tumor location in the breast, which led to the postulate that only these recurrences shoud be prevented, wheras recurrences elsewhere in the breast would represent new primaries. However, some data suggest that, in the long term, WBR can prevent the occurrence of such elsewhere recurrences, the exact nature of which remain to be precisely determined by biological characterization.
- The planned treatment volume defined in most PBI techniques, usually encompasses the vague definition of the surgical cavity with arbitrary margins aimed at treating the microscopic residual disease and taking into account set-up variations and patient's respiratory movement. These definitions vary from one technique to another and are often mostly determined by the constraints of the technique itself. Therefore, the definition of margin in these techniques is highly imprecise.
- Hypofractionation has not been validated in the long term, using these particular regimen. Single doses, or high doses per fraction, with a short repair interval, may lead to increase long-term sequelae in the treated area; models of biological equivalence are not fully reliable, and need to be validated in breast cancer. Recent results from large, randomised multicentric studies of hypofractionated WBR suggest that regimen using 13 to 16 fractions can be safely applied, which are not much different from the 10 or more fractions used in the APBI regimen.

Finally, the technical delivery of whole-breast radiotherapy has dramatically improved in the recent years, allowing in most instances to safely prevent the unnecessary irradiation of organs at risk.
In conclusion, the concept of partial breast irradiation represents a significant shift in the current paradigm of breast-conserving treatment. It raises many unsolved issues that need to be validated in prospective trials, and its effects will have to be measured in the long term. It is much too early yet to determine whether it would be a becomme a valid alternative to whole-breast irradiation in selected groups of patients.

191 INVITED

The effects and interaction by multimodal therapies, radiation, cytostatics and trastuzumab, on cardiac toxicity

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Background: Postoperative radiotherapy reduces the risk for local recurrence with around 2/3. Adjuvant tamoxifen, cytostatics, and combinations with trastuzumab improve overall survival. For many patients, the use of systemic adjuvant therapies have presently to be combined with postoperative radiotherapy in order to obtain the most optimal results, trading of benefits versus increased side-effects.