sel formation (anti-angiogenic drugs), or directed against existing tumor-vasculature (anti-vascular drugs). Among anti-angiogenic drugs the monoclonal antibody bevacizumab blocking VEGF has completed Phase II evaluation showing preliminary antitumor activity (10%) at the cost of some unpredicted toxicity (hypertension). Studies are now ongoing with bevacizumab in combination with chemotherapy in breast cancer. Other anti-angiogenic molecules include inhibitors of tyrosine-kinase receptors for angiogenic peptides, selective metalloproteinase-inhibitors, and endogenous angiogenesis-inhibitors (angiostatin, endostatin). All are at an earlier stage of development, and no evidence of antitumor activity was reported yet. Antivascular drugs contribute to the rapid destruction of existing blood vessels in tumors containing activated endothelial cells. Among these, combretastatins and immunotoxins selectively targeting tumor endothelial cells appear of special promise, although vascular toxicity to the myocardium has been reported and may limit their development. In this wealth of pharmacologic opportunities, the main challenges are those of defining the appropriate way of evaluating the therapeutic benefit of anti-angiogenic/antivascular drugs (long-term control of micrometastases?), and defining the optimal modality of combining them with existing drugs to fully exploit their therapeutic potential.

185 INVITED

Anti receptor antibodies: Update of their current role in the treatment of breast cancer

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The only anti receptor antibody with a current role in the treatment of breast cancer (B.C.) is Herceptin® (trastuzumab), a humanized monoclocal antibody (Mab), produced against the extra cellular domain of HER_2, a type I tyrosine kinase receptor of the HER family.

In the last 16 years the following sequence of critical events has taken place: 1) the cloning of the human HER_2 gene in 1985; 2) the identification of its corresponding protein HER_2; 3) the correlation between HER_2 gene amplification and HER_2 receptor overexpression with an aggressive form of B.C.; 4) the demonstration that the murine Mab 4D5 markedly inhibits the proliferation of human tumor cells overexpressing HER_2; 5) the humanization of 4D5 to produce the drug Herceptin®; 6) the start of Herceptin® clinical trials in 1992; 7) the registration of the drug worldwide for use as monotherapy in patients with HER_2 overexpressing B.C. who have failed anthracyclines and taxanes, as well as upfront use in combination with paclitaxel (1998–2000); and 8) the initiation of large adjuvant randomized clinical trials of Herceptin® (2000–2001).

There is still room for further progress with the use of Herceptin® in the management of B.C.

In advanced disease priorities include: 1) the optimization and standardization of HER_2 testing; 2) the refinement of the Herceptin® administration schedule; 3) the comparison of single agent Herceptin® to Herceptin® plus chemotherapy; 4) understanding the mechanisms of resistance to Herceptin®; 5) the identification of predictive factors linked to Herceptin's cardiotoxicity; 6) and the exploration of combinations of Herceptin® with other targeted therapies. Among these, combinations of Herceptin® with endocrine therapy, with Zarnestra® (a farnesyltransferase inhibitor) or with a preteasome inhibitor will be briefly discussed.

In early disease, close to 12 000 women with HER_2 overexpressing B.C. will be enrolled in four large adjuvant trials investigating the role of Herceptin® given together with or following adjuvant chemotherapy. These trials, with their complimentary designs, should provide a clear answer as to the benefit/risk ratio of adjuvant Herceptin® by 2006–2007.

Thursday, 21 March 2002 14:45–16:15

SYMPOSIUM

Clinical implications of lymphatic mapping by sentinel node biopsy

186 INVITED

Micrometastases: Detection and clinical significance

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About 30% of axillary lymph node (ALN) negative breast cancer patients die of distant metastases despite adequate local therapy. Might more intensive surveillance for subclinical regional or systemic disease uncover this metastatic potential? In breast cancer the search has focused on three sites: 1) the ALN, 2) the bone marrow, and 3) the peripheral blood, and all three have produced exciting developments over the past decade. This presentation addresses the clinical significance of *occult metastases in the ALN*, and topic made particularly relevant by the advent of sentinel lymph node (SLN) biopsy.

Two types of study encompass the literature on micrometastases in breast cancer, 1) those in which patients *classified initially as ALN-positive* are stratified by size of ALN metastasis, and 2) those in which patients *classified initially as ALN-negative* are found on further study to be ALN-positive. Both, given adequate study size and length of follow-up, suggest that micrometastases are prognostically significant. SLN biopsy, a *targeted* examination of an average of 2 ALNs (those most likely to contain metastases), for the first time makes enhanced pathologic analysis by serial sectioning (SS) and immunohistochemistry (IHC) logistically feasible and allows the identification of a group of patients whose risk of systemic relapse might otherwise go unrecognized.

Enhanced pathologic techniques have played at least four undisputed roles in the evolution of SLN biopsy for breast cancer: 1) improved staging of the axilla, 2) validation of the SLN hypothesis, 3) reduction in the rate of false-negative SLN, and 4) the prediction of non-SLN metastases in patients with positive SLN. The prognostic significance of SLN micrometastases remains a subject of controversy. Critics suggest that "micrometastases" 1) are displacement artifact and not biologic metastases, 2) require prospective trials to establish prognostic significance, and 3) should not alter treatment, especially if detected only by IHC.

Breast cancer is a disease characterized by heterogeneity and nowhere is this heterogeneity more apparent than at the level of nodal metastases. "Micrometastases" are not a single entity but comprise a spectrum of pathologic findings, and probably a spectrum of risk. The weight of current evidence is that occult nodal metastases are prognostically significant, but this may in fact only prove true for those patients with a larger volume or number of micrometastases and not single cells detected by IHC. Even with the maturity of prospective trials now in progress, the prognostic significance of occult SLN metastases will remain a matter of debate.

187 INVITED

Sentinel node biopsy or axillary clearance: equal staging and less morbidity? The ALMANAC trial

R.E. Mansel. *Univ. Hospital Wales, Department of Surgery, Cardiff, UK*

The promise of sentinel node biopsy is that it will deliver axillary staging equivalent to axillary node clearance without the well-documented but underestimated morbidity of that procedure. The first part of this promise seems to be deliverable as detection rates for sentinel nodes are greater than 95% in experienced hands with false negative rates of less than 5%,especially with the combined isotope/blue dye method. However, the best results have been reported from high-caseload, experienced centres and the learning curve problem has begun to emerge in some series of low caseload surgeons who have undertaken the technique with a minimum of prior training. The literature suggests that around 30 to 40 audit cases are needed to be sure of producing a high standard. In the multicentre UK study (ALMANAC trial)each surgeon performed an audit set of 40 cases after prior in the unit training supervised by the principal investigator of the trial. The data shows that this approach produced high success rates of around 96% detection of sentinel nodes and a false negative rate of 4.5%, but with an abbreviated learning curve.

The second promise of low morbidity has not yet been proven as few data have been published on this topic. The expectation of reduced side-effects seems to be based more on 'common sense' rather than data.The side-effects of axillary surgery are often underestimated by surgeons, and current measuring instruments are often lacking in detail for axillary symptoms. The ALMANAC group have developed a new axillary subscale to the FACT B-4 quality of life questionnaire,which has been shown to be very sensitive in detecting changes in common axillary symptoms such as sensory disturbance and shoulder stiffness. This new subscale is being used in the randomised phase of the ALMANAC trial,which has currently randomised over 500 patients, to compare the morbidity of conventional axillary surgery with sentinel node biopsy.The definite proof of the advantage of sentinel node biopsy is required since the only rationale for the procedure is a reduction of morbidity over that produced by axillary clearance. Although the symptomatic results will be seen in the near future, the potential problem of increased local recurrence will take longer to emerge.

188 INVITED

Sentinel node negative and no treatment: Is it safe?

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We have been performing axillary sentinel node biopsy (SNB) in breast cancer since 1996. Approximately 3000 patients have undergone SNB at our center approximately 1600 of whom had a negative SN and underwent no further axillary treatment. Among these 516 patients were enrolled in a randomized trial, 259 were randomized to SNB, 166 had a negative SN and did not receive further axillary treatment. Among the 257 patients randomized to axillary dissection, 166 had a negative axilla. After a mean follow up of 26 months, there have been no axillary events among the 166 patients who received SNB. Indicating that no treatment in SN negative cases is at least as safe, from the oncological point of view, as axillary dissection.

Six months after the operation, the intensity of pain, presence of paresthesia, arm mobility, appearance of the axillary scar judged and circumference of the operated arm were assessed in 100 consecutive AD arm patients and 100 consecutive patients who did not receive total axillary dissection as the SN was negative. There was less subjective pain and numbness and better arm mobility in patients who only SNB only.

These data suggest that no treatment of the axilla in SN negative cases safe. An further indicate that routine axillary dissection should be abandoned in favour of SNB. In patients with a negative SN who receive no further treatment the risk of understaging is small and largely compensated for by more accurate histological examination of the SN. A preliminary examination of all 1600 patients who have received SNB so far fully supports the conclusions reached on our trial patients.

189 INVITED

Clinical relevance of sentinel nodes outside the axilla

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The hypothesis is that identification and investigation of sentinel nodes outside the axilla will improve staging and will lead to better outcomes.

Till date, nodal involvement is the best prognostic factor. It has been sufficiently proven that understaging of lymphatic dissemination by insufficient nodal sampling results in inferior survival rates. This may be due to under utilisation of adjuvant systemic treatments or insufficient loco-regional control. From this one can draw the general rule that better-lymphatic-staging will result in better outcomes; either by less over treatment resulting in less morbidity without losing significant survival benefits, or by rightfully applying adjuvant treatments with accompanying survival benefits.

Traditionally, lymphatic dissemination is sought in the axilla. From old mastectomy series including supraradical lymph node dissections with internal mammary chain (IMC) nodes removal, it is well known that IMC dissemination may occur in -larger tumours- up to 20% (5–10% isolated IMC metastases). Further, isolated IMC nodal dissemination caries the same worse prognosis as isolated axillary lymph node metastases. Thus knowing IMC nodal status -or better lymph node status outside the axilla- may enhance prognostic information.

Lymphatic mapping by using lymphoscintigraphy has renewed interest in lymphatic dissemination to extra axillary sites. Interestingly, cutaneous or subcutaneous injection of tracers will hardly ever lead to sentinel nodes outside the axillary regions. Injection of radiolabeled tracers of intermediate particle size (80–200 nm, Nanocolloid) in small volumes in the parenchyma of the breast or in the tumour will lead in 15–25% of the patients to sentinel node outside the axilla, as has been shown by us and a number of series. Extra axillary nodes are located in the internal mammary chain, intramammary infra- or supraclavicular.

We performed lymphatic mapping by preoperative scintigraphy, the use of patent blue dye and intraoperative probe on 606 patients. Lymphoscintigraphy depicted in 27% (164/606) of procedures extra-axillary sentinel nodes. The 119 sentinel nodes depicted in the IMC (18%), 86% (102/119) could be harvested and contained metastases in 17% (17/102). In 52 patients other non-axillary nodes were excised (identification rate of 70%) and 12 (23%) contained metastases. In all, in 3% of all patients extra-axillary lymph node metastases were found while the axillary nodes were negative.

Non-axillary sentinel node biopsy had therapeutic consequences in 5% of the whole population and in 18% of the subgroup with non-axillary drainage. The most apparent therapeutic consequences were: adjuvant systemic treatment in patients considered as good prognosis by an axillary negative nodal status, omitting adjuvant radiotherapy in IMC node negative cases and applying IMC radiotherapy in node positive cases.

Extra-axillary sentinel node biopsy is associated with low morbidity and will improve staging and must therefore improve outcomes.

Thursday, 21 March 2002 14:45–16:15

SYMPOSIUM

Intraoperative radiotherapy: rationale, techniques, results

190 INVITED

Intraoperative radiotherapy: rationale, techniques, results

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In order to avoid a prolonged course of external irradiation, several Authors treated patients with low or high dose-rate iridium implants to the primary tumor bed alone as part of breast conserving protocol. Local control rate was very high (from 92 to 100%) in all trials but one. It is worthwhile to mention that in all trials reported above the cosmetic result was comparable to conventional approach and the incidence of distant metastases and overall survival was similar to those treated with a combined radiation treatment.

The experience on 201 patients treated at the European Institute of Oncology with Intraoperative Radiotherapy as a whole treatment allows a positive preliminary conclusion. The procedure is simple and rapid, the training of the staff easy, the acute side-effects are minimal and not serious. The patients' satisfaction is high, as the long period for the external radiotherapy is avoided.

IORT dramatically reduces radiation exposure of the skin, of the lung, and of the subcutaneous tissues and completely avoids the irradiation of the controlateral breast, contributing to a very low incidence of radiation-induced sequelae.

191 INVITED

Targeted intra operative radiotherapy (Targit) for early breast cancer: Rationale and early clinical experience

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Early local recurrence of breast cancer most commonly (over 90%) occurs at the site of the primary tumour. This is true whether or not radiotherapy is given and irrespective of the margin status. Whole-organ analysis of mastectomy specimens on the other hand, reveals that 63% of breasts harbour occult cancer foci and 80% of these are situated remote from the index quadrant. Therefore, these occult cancer foci may be clinically irrelevant. Hence, after breast conserving surgery, it may not be necessary to treat the whole breast with the usual 6 week long course of post-operative radiotherapy that is not only inconvenient and costly, but may cause many women from geographically remote areas to choose mastectomy. *Targ*eted *i*ntra-operative radio*t*herapy (*Targit*) to the peri-tumoural area alone might provide adequate local control. 'Intrabeam' (*PeC*) is a portable electron-beam driven device that can deliver therapeutic radiation (soft x-rays) in 20–30 minutes within a standard operating theatre environment. The pliable breast tissue - the target - is wrapped around a spherical applicator - the source - providing truly conformal radiotherapy. The prescribed dose is 5 & 20 Gy at 1 cm and 0.2 cm respectively, from the tumour bed. The biologically effective dose is