We will briefly indicate the major issues in retrieving tissues for future research use and in using existing tissue banks for translational research. The main focus will be on the implementation of the informed consent requirement.

## Thursday, 18 March 2004 14:15–15:45

**SYMPOSIUM**

# New developments in systemic adjuvant treatment

**222** INVITED

### Endocrine therapy

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For nearly 20 years, the selective estrogen receptor modulator, tamoxifen, has been the primary agent for adjuvant endocrine therapy for women with steroid receptor-positive breast cancer. New data over the last several years are now challenging this. Recent trials support the use of ovarian suppression/ablation approaches with or without tamoxifen in place of chemotherapy for some premenopausal women. A large randomized trial has established the short-term efficacy and safety of the aromatase inhibitor, anastrozole, in place of tamoxifen for postmenopausal women. A second trial has also supported a role for sequential endocrine therapy as it demonstrated improved short term outcomes for postmenopausal women who received the aromatase inhibitor, letrozole, after completion of five years of adjuvant tamoxifen. How and when to integrate these new findings into standard practice are topics of debate. Ongoing research is focused on the choice of endocrine approach, duration and sequence of therapy, identification of better predictive markers for response to hormone therapy, and evaluation of long-term risks and benefits.

**223** INVITED

### Dose dense chemotherapy for early stage breast cancer

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Combination chemotherapy in the adjuvant setting reduces the risks of relapse and death for patients with invasive breast cancer and adds to the benefits obtained with hormonal treatments [1]. Standard chemotherapy regimens have generally included two or more drugs given over a period of 12 to 24 weeks or longer. In general, anthracycline-containing regimens are superior to those without these agents, treatments longer than six months are not advantageous, and very high dose-regimens – meaning those that require autologous stem cell support – have not proven significantly or consistently superior [2]. Against this background, the development of the taxanes in the 1990s was important because these drugs appeared to be non-cross resistant, had partially non-overlapping toxicities, and were highly active. Hence, many adjuvant therapy trials testing the value of taxanes were developed and are now providing information on their role. To date, nearly every adequately sized and adequately followed trial testing these agents (paclitaxel and docetaxel) in the adjuvant or neoadjuvant setting has been positive and a role for them is broadly accepted [3–8].

Optimizing chemotherapy requires providing the maximal possible benefit at an acceptable level of toxicity. Kinetic modeling suggests that for many drugs dose-escalation beyond a threshold may not be necessary, that combination therapy may sometimes merely add toxicity without benefit, and suggests that sequential treatment applications may provide all of the benefits of combination treatment without the risk of additive side effects [9–11]. By choosing sequential chemotherapy plans we are also able to consider alterations in schedule of administration designed to increase cell kill by diminishing the time between treatments when sensitive clones might re-grow. The availability of granulocyte-colony stimulating factor was critical to the development of this approach as myeloid toxicity is dose-limiting for many of the active agents for breast and other cancers [12].

CALGB 9741 was designed to put these theoretical concepts to the test in a clinically relevant setting. Post-operative patients with node-positive breast cancer were randomly assigned using a factorial design to answer two questions [13]. One concerned the relative value of sequential single agents using active doses of doxorubicin, paclitaxel, and cyclophosphamide compared to a more "conventional" doxorubicin plus cyclophosphamide ("AC") combination followed by paclitaxel. Every patient was to receive four treatments using the same dosing of each of the three drugs. At the first protocol-stipulated analysis point there was no difference for the two treatment schemes supporting the hypothesis that combination therapy is not necessarily superior to sequential single agents. The second question concerned dose-density. All 2005 patients were randomized to receive their assigned treatment regimen at standard 3 week intervals or, utilizing G-CSF support, 2 week intervals. Two week treatment intervals resulted in a statistically significant reductions in the risks of relapse and death, the primary and secondary endpoints of the study. Moreover, there was little or no increased toxicity seen with the increased dose-density. In some regards it was less toxic as it was associated with a reduction in the risk of hospitalization for neutropenic fever. Hence, in CALGB 9741 dose-dense treatment was shorter, safer, and more effective. Planned studies will attempt to build on these observations.

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**224** INVITED

### Optimal integration of chemo-endocrine treatment

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Chemotherapy in association with (usually followed by) endocrine therapy are considered an appropriate treatment option in the adjuvant treatment of patients with endocrine responsive tumors. Combined chemoendocrine therapies with tamoxifen and an anthracycline-based regimen were proven to yield better disease-free survival than endocrine therapy alone in patients with ER-positive tumors. The combination of tamoxifen with CMF-type regimens was superior to tamoxifen alone in trials using the "classical" CMF regimen. Laboratory studies have demonstrated that chemotherapy cell kill was inhibited in the presence of tamoxifen. Results from Clinical Trials also suggested a negative interaction between cytotoxics (alkylating

agents and 5-fluorouracil) and tamoxifen, and a modulation of the interaction by the degree of endocrine responsiveness. Three randomized trials showed the superiority of sequential over concurrent administration of anthracycline-based regimen and tamoxifen for postmenopausal women with node-positive, receptor-positive disease. Although available data indicate the superiority of sequential tamoxifen over concurrent administration, evidence exists on benefit for delayed chemotherapy during tamoxifen for postmenopausal women with node-positive disease. A very large randomized clinical trial has shown preliminary evidence that anastrozole is at least as affective as tamoxifen as adjuvant therapy after chemotherapy for postmenopausal women, 84% of whom had disease recorded as receptor positive. No information is available on the concurrent use of aromatase inhibitor and chemotherapy and the issue is under investigation. In premenopausal women, overview data showed that the administration of goserelin reduced the odds of recurrence and death. Experimental information and preliminary data from phase II trials and phase III Trials suggest that concurrent administration of LH-RH analogue and chemotherapy might improve therapeutic results. The addition of LH-RH analogue to tamoxifen plus or minus concomitant CMF chemotherapy resulted in better results if compared with no LH-RH analogue. A small trial on concomitant ovarian suppression and anthracycline-containing chemotherapy followed by tamoxifen versus endocrine therapy alone provided similar benefit. The sequential use of goserelin following CMF improved outcome compared with either modality alone in patients with node-negative disease, at least in subset analyses, and a trend in favour of the addition of LH-RH analogue after CAF chemotherapy was observed in a large trial (node-positive disease). Optimal integration of endocrine therapy with chemotherapy is a crucial component in decision-making for treatment choice for patients with endocrine responsive tumors and should be further studied in the laboratory and in Clinical Trials.

## Thursday, 18 March 2004 14:15–15:45

**SYMPOSIUM**

# Progress towards loco-regional treatment tailoring

**225** INVITED

### How much can new imaging modalities improve tumour staging?

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A variety of approaches are available to allow more accurate staging. The approaches for presurgical chemotherapy are different to those needed for the patient who is to have definitive surgery. Assessment of tumour extent in invasive ductal carcinomas, invasive lobular carcinoma and ductal carcinoma in situ all require different approaches for accurate staging. Successful chemotherapy prior to surgery makes staging more difficult as it is often difficult to differentiate residual tumour from fibrosis using anatomical imaging methods whilst functional imaging cannot exclude microscopic residual disease. Minimally invasive interventional techniques such as laser and radiofrequency ablation as well as high intensity focused ultrasound all require more accurate imaging information if they are to replace conventional surgery as the main therapy for primary breast cancers.

One of the problems is providing a simple guide for surgeons to allow minimal surgery with good first time excision of all the tumour. More accurate loco regional staging could help to reduce both operating time and number of operations. Effective staging usually needs a multimodality approach with the placement of either intramammary markers or effective skin markers as well as good delineation of sentinel lymph nodes. All modalities except ultrasound require complex procedures to show exact tumour position and the larger the breast the greater the difficulty with all modalities to accurately delineate tumour extent pre-operatively.

The increased use of chemotherapy prior to surgery or alone with radiotherapy, as well as new minimally invasive ablation techniques, also requires much more accurate measurement of tumour extent and stage both prior to and during treatment to provide accurate estimation of therapy response.

In the breast mammography alone is usually sufficient if the breast is mainly fat. The presence of dense stroma immediately reduces mammographic accuracy. In the dense breast ultrasound is more accurate for assessing invasive tumour size than mammography. It can also provide information on axillary lymph node staging especially proof of lymph node involvement if FNAC or core biopsy is used to confirm presence of malignant tissue. Ultrasound accuracy is dependant both on operator experience and imaging quality.

MR has high sensitivity for detection of multifocal and contra lateral disease but its false positive rate requires biopsy proof of additional tumour foci. It shows good correlation with tumour size and may be the best modality currently for showing extent of DCIS. Nuclear medicine currently is most useful for aiding sentinel node biopsy, both axillary and parasternal. Because of its high specificity its place is sorting out complex cases where there is doubt with the help of MIBI and FDG PET.

New imaging techniques are being developed which may help loco regional staging accuracy to increase conspicuity of tumour margins and satellite lesions. They include: mammography (3-D and tomography), ultrasound (3-D, ultrasound contrast agents and novel RF data processing such as used in elasticity imaging), MR (new sequences, coils, contrast agents, elasticity imaging) and nuclear medicine (PET, high resolution cameras, FDG, FLT, oestrogen analogues and other new tracers) as well as other new imaging modalities (multislice CT perfusion imaging).

**226** INVITED

### Minimally invasive techniques in breast cancer treatment

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For almost a century, the treatment for breast cancer was radical surgery. Today, the surgical management of breast cancer is evolving toward minimally invasive procedures. Breast conservative surgery is now the choice for early breast cancer and the acceptance of axillary lymph node dissection (ALND) as part of the management of breast cancer is also decreasing because the increasing use of screening mammography is detecting more small primary lesions with less likelihood of node involvement. Sentinel lymph node biopsy has been taking over ALND in those patients with early stage breast cancer. However, before abandoning ALND, some issues need to be resolved and there are situations where sentinel lymph node still need to be done in the context of clinical trials such as patients with multicentric disease or neoadjuvant chemotherapy.

The increasing use of breast ultrasound (US) has paralleled the increase in the number and quality of screening mammograms. In the past, breast US has been the solely in the diagnostic armamentarium of the radiologist. Ultrasound has now come into play in every aspect of breast surgery, and is being used to characterize, percutaneously aspirate, biopsy, remove or ablate lesions. Breast surgeons with an understanding of the physics and characteristics of benign and malignant lesions have developed US as an extension of the physical examination and an added tool to achieve cancer-free lumpectomies (Figure 1).

There are other techniques that are being explored to make breast surgery less invasive. These include cryosurgery, laser ablation guided by magnetic resonance imaging, and radiofrequency ablation. The goal of these techniques is to destroy by heating or cooling not only the tumor cells but also the surrounding tissue so the lesion can be treated with negative margins. The advances in the field of molecular genetics will help in accomplishing this goal. Until long term results become available clarifying local recurrences and survival, patients should receive these techniques under clinical trials.

Surgeons need to move into the development of all these new techniques for breast cancer treatment because this minimally invasive techniques are becoming a part of the multidisciplinary approach of breast cancer patients.

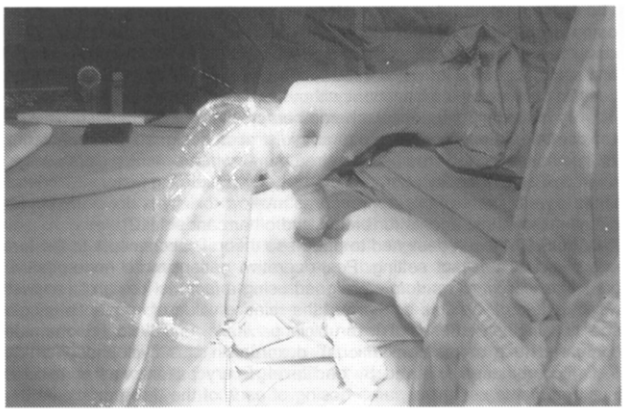

Fig. 1. Intraoperative ultrasound guided breast biopsy.