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