Introduction
Over one million cases of breast cancer are diagnosed each year. While most cases are early stage and curable in the developed world; still up to one-third ultimately develop clinically detectable metastatic disease. Adjuvant systemic therapy reduces that risk thereby improving overall survival.

There are three standard components to adjuvant therapy: poly-chemotherapy, hormone therapy, and immunotherapy. We will review current standard approaches in each of these areas.

Poly-Chemotherapy
CMF was the initial standard, augmented by the addition or substitution of an anthracycline. More recently, the taxanes were added to this program. The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) confirmed the efficacy of CMF and then the incremental benefits of the anthracyclines. Their meta-analysis of the taxane-containing regimens is anticipated but a smaller one already shows no clear association with nodal status, specific taxane, or ER and HER2 status.

- The Impact of Dose and Scheduling on Adjuvant Chemotherapy Strategies
Simple dose-escalation beyond tolerable standard levels has not yielded significant benefits but did increase toxicity. An alternative approach, called “dose-density” utilized similar technological advances including the development of growth factors in particular, to shorten inter-treatment intervals while maintaining standard dose-levels. This approach has been validated in randomized clinical trials and dose-dense AC followed by paclitaxel is a standard approach when these agents are used.

This approach represents a translational therapy success as the rationale is based on the Norton-Simon model which uses mathematical analyses to predict growth and treatment response patterns in tumor systems.

A related approach, also shown to be advantageous; substitutes low dose weekly paclitaxel in place of the conventional three weekly dosing. While not strictly a trial of dose-density (because the dose size was reduced) this is consistent with the predictions of the Norton-Simon model.

- Concurrent versus Sequential Therapy
Based on successes in other malignancies, medical oncologists have been motivated to combine cytotoxic drugs and this approach has been successful. CMF and later AC and other regimens are the result of this approach. However, when the taxanes were added to standard regimens the older debate about the advantages and disadvantages of lower dose concurrent therapy versus higher dose sequential plans were reignited. One advantage of sequential therapy is that it maximizes dose-density as described above. Recent studies suggest that sequential plans, in general, provide maximal benefits but in some cases the results of clinical trials are less definitive. There are no well controlled studies in which a concurrent treatment plan is more effective than a an appropriately matched sequential one.
Hormone Therapy
Adjuvant hormone therapy is effective when the estrogen and/or progesterone receptor are present. For young (pre-menopausal) patients this can consist of tamoxifen and possibly ovarian suppression. The role of ovarian suppression is surprisingly unclear as it is effective in isolation but of uncertain value following conventional chemotherapy. While aromatase inhibitors are clearly indicated for postmenopausal women, their optimal implementation (replacing or following tamoxifen) and duration is not established. They have different toxicities compare to tamoxifen but have only demonstrated a significant survival impact in a limited number of studies. The use of aromatase inhibitors in premenopausal women requires certainty regarding menopause and compared to tamoxifen and ovarian suppression has not demonstrated any advantages. An important issue, still being addressed, is the reliability and reproducibility of hormone receptor testing. Clearly the appropriate use of hormone therapies relies on this critical step.

Chemotherapy and Hormone Therapy Combinations
Our growing recognition of the heterogeneity of breast cancer, both phenotypically and in terms of treatment responsiveness, has led to a careful reconsideration of the former “one size fits all” approach. For triple negative breast cancer, only chemotherapy is an option. For HER2 positive breast cancer, chemotherapy and trastuzumab are generally required. But for the largest subset of patients with HER2 normal, hormone receptor positive tumors, the role of chemotherapy added to hormone therapy is undergoing careful reconsideration.

While AdjuvantOnline! and other tools have been developed to help clinicians manage individual patients, genomic sub-typing is probably the most promising approach to treatment individualization. There are a range of genetic and phenotypic tests currently available and while none has been fully validated. The two that are most widely considered are the prognostic test – Mammaprint – and the predictive test (for chemotherapy responsiveness) – OncotypeDx. If available the Mammaprint can stratify individual patients, regardless of receptor profile, as high or low risk. The OncotypeDx Recurrence Score is limited to patients with hormone receptor positive disease but it predicts the utility of adding chemotherapy. Each of these tests is currently the focus of randomized prospective studies.

Anti-HER2
The development of trastuzumab and then lapatinib, followed by a large number of innovative HER2-targeting agents represents a triumph of modern science and translational medicine. The impact of trastuzumab in the adjuvant setting is significant such that the current focus of clinical trials is on the treatment of the patients with very small or otherwise “lower risk” tumors, and the elderly. At the same time, we are exploring the incremental value of adding or substituting additional anti-HER2 agents. For patients with HER2 positive disease, the critical intervention is the use of trastuzumab. Most studies have relied on a combination with a taxane and one year of antibody therapy. Outside of a clinical trial, oncologists should not routinely deviate from this approach. As is true with hormone receptor testing, accurate assessment of the marker (HER2) is a critical component of care.
Conclusion
Advances in systemic adjuvant therapy continue. Improvements in our use of the oldest approach – hormone therapy – continue. For chemotherapy we have newer agents (i.e., eribulin) to consider and we continue to optimize the application of existing drugs. And targeting of oncogenic drivers of cancer, like HER2, have begun to yield impressive results. The superimposed use of genomic testing will improve our patient and treatment selection and further enhance the value, risk/benefit ratio, and efficacy of adjuvant therapies.

Suggested Reading