Perspectives

from an Oncologist in an Outpatient Oncology Clinic

by Gershon Y. Locker, MD, FACP

The papers presented at ASCO 2006, while not revolutionary in their impact, will lead to some evolutionary changes in the practice of oncology. For this article, I did not review some of the most exciting presentations, such as STAR (Study of Tamoxifen and Raloxifene) in the prevention of breast cancer, because they will not have a direct effect on practice in the cancer clinic. Likewise, I will not discuss some of the basic science advances not yet near clinical release. If any recurrent themes exist in the following discussion, they are the use of more oral agents and targeted treatments and fewer IV chemotherapy drugs, and more challenges to conventional wisdom.

Breast Cancer

For the second year in a row, the treatment of the 20 percent of women with breast cancers over-expressing HER2 will be changed as a result of ASCO presentations.

To date, the standard of care is to continue trastuzumab (Herceptin), but change chemotherapy after failure of first-line chemotherapy plus trastuzumab for metastatic disease. At ASCO's *Clinical Science Symposium*, lead researcher Charles Geyer, MD, reported that lapatinib, an inhibitor of the HER2 (and HER1/EGFR) receptor tyrosine kinase, when added to capecitabine (Xeloda) is more effective (time to progression) than capecitabine alone after failure of previous trastuzumab plus chemotherapy. This finding suggests an alternative approach of changing *both* the chemotherapy and the targeted therapy for second treatment of advanced HER2 positive disease. The substitution of an oral agent for one of the most expensive IV agents administered in the outpatient clinic could have a major impact on both patients and the clinics.

Ancillary testing and medications are also a major issue for both breast cancer patients and hospital cancer centers. Aromatase inhibitors (AIs) are increasingly being used in the adjuvant treatment of post-menopausal women with early stage breast cancer. Unfortunately, AIs are associated with an increased risk of osteoporosis and fracture.

Abstract 511 reported the 5-year results of the ATAC (Arimidex, Tamoxifen Alone or in Combination study) bone sub-protocol, which assayed risk of osteoporosis by serial DEXA (dual energy X-ray absorptiometry) scans. None of the women who had a normal baseline DEXA scan developed osteoporosis after 5 years of anastrozole; only 15 percent of women with baseline osteopenia developed osteoporosis. The implications for women with normal baseline bone density who are to begin anastrozole are that aggressive DEXA monitoring and prophylactic bisphosphonates are not appropriate. Even for patients with mild osteopenia, physicians are not necessarily obligated to start expensive bisphosphonates.

Colorectal Cancer

The treatment of advanced colorectal cancer with oxaliplatin- or irinotecan-based therapies has led to marked improvement in survival. Continuous administration of chemotherapy, however, is associated with cumulative treatment-limiting toxicity. Two papers presented at ASCO suggest that treatment vacations are safe and desirable in select patients.

Abstract 3504 reported that continuous OPTIMOX (six FOLFOX7 treatments alternating with six 5FU/LV2 treatments), while associated with a longer progression-free survival than intermittent FOLFOX7, was no different in overall duration of disease control.

Abstract 3505 found that continuous FOLFIRI was no better than intermittent FOLFIRI (2 months on/2 months off) in terms of progression-free or overall survival. It is likely that a large number of patients with advanced colorectal cancer who have shown good responses to chemo can be offered chemotherapy vacations. (The role of targeted therapies as maintenance is under study). This scenario could have ramifications for outpatient chemotherapy volume in the short term.

Abstract 3510 may lead to some practice alterations for those patients getting oxaliplatin-based chemotherapy first line for metastatic disease. The final analysis of the TREE trial initially compared modified FOLFOX6 to bFOL (weekly FU/leucovorin plus q2wk oxaliplatin) to CAPEOX. After 150 patients were enrolled, bevacizumab (Avastin) was added to all three arms and the CAPEOX dose decreased.

Although small, the study strongly suggested three findings. First, that bolus 5FU/leucovorin was inferior to infusion FU when given with oxaliplatin. Second, that adding bevacizumab, no matter what the regimen, improved response rate and survival. Lastly, that when both regimens are given with bevacizumab, modified CAPEOX was equivalent to FOLFOX6 in response rate and survival. The TREE trial suggests more substitution of capecitabine for infusion FU and more bevacizumab overall. If adopted by practitioners, both findings will have definite implications for resource utilization and finances of the hospital clinic.

One of the common biases in oncology is the assumption that elderly patients tolerate standard chemotherapies poorly. *Abstract 3517*, a retrospective pooled analysis of four trials evaluating FOLFOX as therapy for both advanced and early stage colorectal carcinoma, looked at whether there was any difference in efficacy or tolerance in the elderly (≥70) compared to younger patients.

The study found an increase in grade 3/4 neutropenia

(49 percent vs. 43 percent, p=0.04) and thrombocytopenia (5 percent vs. 2 percent, p=0.04). However, the study found no significant difference in non-hematologic toxicity, including neurotoxicity, nor in benefit of FOLFOX, or in median dose intensity. Suggesting little need to avoid FOLFOX in the adjuvant or metastatic setting in the healthy elderly for whom treatment is appropriate; these findings will definitely affect clinic volume.

Pancreatic Cancer

Advanced pancreas cancer Phase II studies have suggested that fixed dose rate (FDR) gemcitabine (Gemzar) or gemcitabine plus oxaliplatin (Eloxatin) might be superior to standard gemcitabine. This finding led many clinicians to use these two newer regimens.

Abstract 4004 reported on the results of the ECOG trial, which compared standard gemcitabine to FDR gemcitabine to FDR gemcitabine plus oxaliplatin. The study found no significant difference in efficacy between standard gemcitabine and the experimental treatments, although there was a borderline trend to survival superiority for the FDR gemcitabine arm. Given the additional toxicity and resource utilization of the two experimental arms and the limited, if any, additional benefit, their use routinely in the outpatient clinic is likely to decline.

Lung Cancer

The lung cancer paper likely to impact treatment in the outpatient clinic was the updated analysis of CALGB 9633 (*Abstract 7007*). Since 2004, when it was first reported as a positive trial for disease-free and overall survival, adjuvant chemotherapy has become a standard of care for patients with Stage IB non-small cell lung cancer (NSCLC). The updated CALGB 9633 randomized patients with resected Stage IB NSCLC to no further therapy or paclitaxel (Taxol) plus carboplatin (Paraplatin). In contrast to the earlier report, the study found no overall survival benefit with the chemotherapy (HR=0.80, CI=0.60-1.07, p=0.1), nor a 5-year survival benefit, although there was still a disease-free survival benefit (HR=0.74, 0.57-0.96, p=0.027).

Similarly, *Abstract 7008* reported a meta-analysis of five large randomized studies of cisplatin-based adjuvant chemotherapy in non-small cell lung cancer. While the study found a survival benefit in stage II disease, there was no significant overall survival benefit in Stage Ib disease (HR=0.9, 0.78-1.10).

Both studies suggest we will likely see a decrease in the use of adjuvant therapy in patients, other than on research trials, for Stage I lung cancer.

Prostate Cancer

The timing of radiotherapy for patients with PSA-only relapse after radical surgery for prostate cancer is problematic.

Abstract 4514 provided a mathematical model to predict the 6-year likelihood of progression-free survival (PFS) following salvage radiotherapy for men with biochemical relapse after radical prostatectomy. The data was striking. Overall, the 6-year PFS was 32 percent; but for patients radiated when the PSA was 0.5 or less, PFS rose to 48 percent, with a median PFS of 69 months. This finding strongly suggests that when the PSA is less than 0.5, salvage radiation should be done for patients who are candidates.

As with women with breast cancer, adjunctive hormonal therapies can be associated with osteoporosis in men with prostatic cancer. *Abstract 4515* was a small study that looked at the use of the bisphosphonate, zoledronic acid, in men receiving GnRH (gonadotropin-releasing hormone) agonists for non-metastatic prostate carcinoma. Patients were randomized to placebo or a single dose of zoledronic acid. Bone mineral density was measured at baseline and one year later. Men on the treatment arm had preserved or increased bone mineral density compared to men on the placebo arm who had bone loss in lumbar spine and hip. Bottom line: a single yearly dose of the IV bisphosphonate seems a reasonable therapy for men on GnRH agonists with non-metastatic prostate cancer.

Two papers presented in a plenary session of ASCO 2006 are changing the paradigm for the treatment of advanced renal cancer.

Renal Cancer

Two papers presented in a plenary session of ASCO 2006 are changing the paradigm for the treatment of advanced renal cancer. Until this year, interferon and interleukin were the only drugs with established activity approved in that disease; however, both drugs were associated with significant side effects.

Abstract 3 presented the results of a randomized Phase III trial of sunitinib, a tyrosine kinase inhibitor of VEGFR, ckit, PDGFR, versus interferon alpha in previously untreated patients with advanced renal cell carcinoma. Sunitinib was associated with three key findings:

- A significantly longer progression- free survival (47.3 versus 24.9 weeks p<.000001)
- A higher response rate (24.8 percent vs. 4.9 percent p<.000001)
- A better toxicity profile.

Likewise, *Abstract 4*, was a randomized study of temsirolimus versus interferon, versus the combination in previously untreated patients with advanced renal cell carcinoma. TEMSR (temsirolimus) inhibits mTOR, a signaling protein involved in cell growth and angiogenesis. Patients treated with TEMSR alone had a statistically significant longer overall survival than patients treated with interferon (10.9 vs. 7.3 mo HR=0.73, CI 0.57-0.92). Patients experienced no survival difference between the interferon alone and the interferon plus TEMSR arms. Asthenia was the major TEMSR-associated toxicity (27 percent grade 3 or greater).

These two papers, coupled with the recent reports of activity of sorafenib and bevacizumab in advanced renal carcinoma, have changed that disease in the last year from one with few active drugs with great toxicity to one with several active agents with acceptable side effects. The effect of all of these new agents on cancer care is unclear, but it is likely that less interferon will be used in the metastatic disease setting.

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