Reports from the 2010 ASCO Annual Meeting

The 2010 Annual Meeting of the American Society of Clinical Oncology (ASCO) was held in Chicago, IL, from June 4–8, 2010. Results from this meeting have been published in many outlets, and the major results have been made readily available. In this section, members of the *JAdPrO* Editorial Board have selected and summarized a number of studies—including some that did not receive major media attention during the first week of June—thought to be of particular interest to advanced practitioners in oncology.

Brain Cancer

Survival of elderly patients (≥ 60 years) with glioblastoma is short, and the benefit of standard radiation therapy remains controversial in this patient population. Published level 1 evidence of temozolomide (Temodar) and radiotherapy used concurrently in newly diagnosed glioblastoma patients did not include patients ≥ 70 years of age. In clinical practice, a more protracted course of radiation therapy (i.e., 2 weeks) or use of chemotherapy often is recommended. Two studies evaluating the efficacy of therapy were presented, with conflicting results. Ongoing phase III trials that include elderly patients should provide guidance regarding treatment in this population. Results from use of bevacizumab (Avastin) with and without irinotecan also were discussed.

PROLONGED RADIOTHERAPY

In a study by Malmstrom and others (2010), 42 patients with newly diagnosed glioblastoma who were ≥ 60 years of age were randomized to receive either standard radiotherapy (60 Gy in 2-Gy fractions over 6 weeks), hypofractionated radiotherapy (34 Gy in 3- or 4-Gy fractions over 2 weeks), or 6 cycles of chemotherapy with 200 mg/m^2 of temozolomide given on days 1 to 5 every 28 days. The primary study endpoint was overall survival (OS).

There was no significant difference in OS between the three treatment arms. The median OS was 6 months for the group receiving standard radiotherapy, 7.5 months for patients given hypofractionated radiotherapy, and 8 months for those given temozolomide.

The authors concluded that prolonged radiotherapy provided no benefit when compared with standard radiotherapy or use of chemotherapy. These results suggested that standard radiotherapy should no longer be offered to elderly glioblastoma patients; exclusive temozolomide may be considered as an alternative.

INTERMITTENT TEMOZOLOMIDE VS. INVOLVED-FIELD RT

Wick et al. (2010) reported on the Neuro-oncology Working Group (NOA)-08 trial of the German Cancer Society, which involved 373 patients > 65 years of age who were diagnosed with anaplastic astrocytoma or glioblastoma. The investigators compared standard radiation therapy (6 weeks to a dose of 54 to 60 Gy) with 100 mg/m^2 of temozolomide given on a 1-week-on/1-week-off schedule, with dose modification in 25-mg steps in both directions. The primary endpoint was median OS.

Patients treated with temozolomide alone had an increased risk of death (hazard ratio: 1.24; 95% confidence interval [CI], 0.94–1.63) compared with those who received radiation. Patients in the temozolomide arm had a higher rate of adverse, serious events than did those in the radiotherapy arm.

This trial did not show dose-intensified temozolomide alone to be inferior to radiotherapy alone in the primary treatment of elderly patients with malignant glioma. Radiotherapy cannot be deferred safely in the treatment of older patients with anaplastic astrocytoma or glioblastoma.

EFFICACY AND SAFETY OF BEVACIZUMAB WITH OR WITHOUT IRINOTECAN

The US Food and Drug Administration (FDA) has approved use of bevacizumab to treat glioblastoma. This study reports on the OS and toxicity in participants in the BRAIN study (Cloughesy, Vredenburgh, Day, Das, & Friedman, 2010), a phase II, open-label, multicenter, randomized, noncomparative trial of 85 patients with glioblastoma at first or second relapse who were treated with bevacizumab and 82 patients who were treated with bevacizumab and irinotecan. Patients using bevacizumab whose disease progressed and

who met eligibility criteria could enroll in a postprogression phase to receive bevacizumab and irinotecan.

The median OS was 9.3 months (95% CI [8.2, 11.8]) in the bevacizumab arm and 8.9 months (95% CI [7.9, 11.9]) in the combination therapy arm. The OS at 40 months was 11% in the bevacizumab arm and 16% in the combination therapy arm. Adverse events ≥ grade 3 occurred in 51.2% and 70.9%, respectively; they included hypertension (10.7% vs. 3.8%), cerebral hemorrhage (0% vs. 1.3%), venous thromboembolism (3.6% vs. 10.1%), and arterial thromboembolism (3.6% vs. 2.5%); gastrointestinal (GI) perforation occurred in 2.5% of patients in the bevacizumab/irinotecan arm.

This updated survival data showed an incidence of selected adverse effects that was consistent with that previously reported and identified no new safety signals.

Colorectal Cancer

Recent years have brought considerable information on the role of genetics in the selection of colorectal cancer treatment, the importance of markers in designing effective treatment plans, and the efficacy of combination drug regimens in treating this disease. Investigators discussed modified use of 5-fluorouracil/leucovorin/oxaliplatin (mFOLFOX6) with or without cetuximab (Erbitux) in V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog *(KRAS)* wild-type patients, identification of specific factors in stages II and III colon cancer, and the use of first-line capecitabine (Xeloda)/oxaliplatin (XELOX) followed by bevacizumab with or without XELOX in metastatic colon cancer.

mFOLFOX6 WITH OR WITHOUT CETUXIMAB IN *KRAS* WILD-TYPE PATIENTS

As the armamentarium for systemic treatment of colorectal cancer has expanded, clinicians continue to have questions regarding the most efficacious chemotherapy/targeted therapy combinations and how drugs should be sequenced. In 2005, the FDA approved the FOLFOX regimen for use in the adjuvant colorectal cancer setting. To investigate the efficacy of cetuximab in combination with mFOLFOX6 in this setting, Alberts and colleagues (2010) conducted a trial in *KRAS* wild-type, stage III colon cancer patients who underwent resection.

Adjuvant cetuximab does not improve survival in stage III colon cancer.

Planned accrual was 2,070 patients. Interim analyses were performed after 25%, 50%, and 75% planned events. In all, 1,760 patients were randomized to receive mFOLFOX6 with or without cetuximab for a total of 12 biweekly cycles. The primary endpoint was disease-free survival (DFS). Secondary endpoints included OS and toxicity. The median follow-up of 1,624 patients was 15.9 months.

The trial was closed to accrual following the preplanned interim analysis after 50% of planned events demonstrated no benefit with added cetuximab. Patients given mFOLFOX6 plus bevacizumab had significantly greater incidences of any adverse events ≥ grade 3, diarrhea, and failure to complete 12 cycles.

The investigators concluded that adding cetuximab to mFOLFOX6 was not beneficial for *KRAS* wild-type patients with resected stage III colon cancer.

XELOX AND BEVACIZUMAB IN METASTATIC COLON CANCER

Questions remain regarding the optimal duration of first-line therapy for metastatic colorectal cancer after maximal response has been attained. In the MACRO trial, Tabernero and colleagues (2010) evaluated the efficacy and tolerability of XELOX plus bevacizumab given for 6 cycles followed by XELOX plus bevacizumab (arm A) or bevacizumab alone (arm B) as maintenance therapy in metastatic colorectal cancer patients. The primary endpoint was progression-free survival (PFS), with secondary endpoints of OS, objective response rate, and safety.

A total of 480 patients enrolled in this trial were evenly distributed between arms A and B; there were no significant demographic differences between the groups. Median follow-up was 16 months. There were no statistically significant differences in PFS, OS, and objective response rate between the two arms. Median PFS was 11 vs. 10 months, respectively; median OS was 25.3 vs. 20.7 months; and the objective response rate was 60% vs. 57%. Preliminary

analysis showed grade 3/4 diarrhea in 11% of those in arm A vs. 13% of those in arm B; hand-foot syndrome occurred in 12% vs. 6%, respectively; and neuropathy was reported in 24% vs. 7%, respectively.

Induction therapy with XELOX plus bevacizumab followed by maintenance bevacizumab was noninferior to continuation of combination therapy. However, further studies evaluating bevacizumab after standard chemotherapy in metastatic colorectal cancer still are needed.

Gynecologic Cancers

GOG 218, a phase III trial, compared intravenous (IV) paclitaxel, carboplatin, and bevacizumab with the standard combination of IV paclitaxel/carboplatin in 1,873 women with advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (Burger et al., 2010). The objective was to determine the therapeutic impact of using concurrent and/or maintenance bevacizumab with standard chemotherapy.

Effectiveness of treatment was measured in terms of survival without evidence of cancer growth (PFS), OS, and quality of life. Patients with stage III or IV ovarian cancer, primary peritoneal cancer, or fallopian tube cancer were randomized to one of three arms, all of which included 175 mg/m^2 of paclitaxel IV over 3 hours and IV carboplatin (area under the curve of 6) over 1 hour. Infusions were given on day 1 of a 21-day cycle. Regimen 1 included paclitaxel and carboplatin IV for cycles 1 to 6 and then placebo for cycles 2 to 22. Regimen 2 included paclitaxel and carboplatin with 15 mg/kg of bevacizumab IV for cycles 2 to 6 and then placebo for cycles 7 to 22. Regimen 3 used paclitaxel and carboplatin with 15 mg/kg of bevacizumab IV for cycles 2 to 6, then maintenance therapy with 15 mg/kg of bevacizumab IV for cycles 7 to 22.

The investigators found no significant increase in the duration of PFS when they compared patients given carboplatin, paclitaxel, and placebo (regimen 1) with those given chemotherapy with 5 cycles of bevacizumab and then extended placebo treatment (regimen 2). However, there was a statistically significant improvement in PFS of 3.8 months for patients randomized to the standard chemotherapy with bevacizumab followed by extended bevacizumab. This result translated into a 28% reduction in cancer progression over standard chemotherapy, or 14.1 months longer without disease recurrence, as compared with 10.3 months for women on chemotherapy alone and 11.2 months for women who had bevacizumab with chemotherapy and no maintenance therapy. The side-effect profile was consistent with that of other bevacizumab studies, with hypertension, GI perforation, and hemorrhage related to use of the monoclonal antibody.

Targeted therapy extends progression-free survival in advanced ovarian cancer.

This study showed that frontline therapy for advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer with standard-of-care chemotherapy plus concurrent and maintenance bevacizumab prolonged PFS. The authors noted that bevacizumab was the first antiangiogenic agent to demonstrate such benefit in this patient population.

Non-small Cell Lung Cancer (NSCLC)

During the Plenary Session of ASCO, Bang et al. (2010) reported on a potentially significant breakthrough in the treatment of NSCLC. A single-arm, first-in-patient study demonstrated the effectiveness of PF-02341066 (crizotinib), a dual-selective inhibitor of anaplastic lymphoma receptor tyrosine kinase (ALK) and Met proto-oncogene (hepatocyte growth factor receptor; c-MET), in 82 patients who tested positive for the ALK fusion protein.

The potentially oncogenic ALK fusion protein results from chromosomal inversion and/or translocation. Prior laboratory data suggested that it might have a role in inhibiting cell growth and inducing apoptosis. In this clinical trial, 82 *ALK*-positive patients received 250 mg of the drug orally twice daily. There were no limits to previous treatment; however, 80% of patients were treatment-naïve, and treated brain metastases were allowed. Performance status ranged from 0 to 3, and the majority of patients were never-smokers (76%). Histology

in 96% was adenocarcinoma.

Crizotinib was well tolerated. Most adverse events were grade 1 or 2 and primarily were nausea (54%), diarrhea (48%), vomiting (44%), and visual disturbance (42%). At a median follow-up of 6.4 months, 6-month PFS survival was 72%. A majority of patients (77%) remained on crizotinib.

Unfortunately, probably only about 5% of NSCLC lesions express the echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK* fusion gene. Nevertheless, this therapy shows promise for *ALK*-positive individuals, and such research paves the way for further development of targeted therapies for NSCLC.

Prevention

Prevention studies are expensive, have extended durations, and may have difficulty accruing patients. However, the information garnered by such research may spare countless patients from the pain and complications of cancer treatment.

ATORVASTATIN TO PREVENT BREAST CANCER

Atorvastatin is a statin that inhibits 3-hydroxy-3-methylglutaryl-coenzyme A reductase. It is currently approved to treat hypercholesterolemia, but preclinical studies revealed that atorvastatin inhibits the growth of breast cancer cells. Ongoing studies are evaluating the effects of atorvastatin in treating non-Hodgkin's lymphoma, melanoma, and breast cancer.

Wood and others (2010) are conducting a study in which premenopausal women (> 34 years of age) at higher risk for breast cancer because of family history, breast cancer *(BRCA)* gene positivity, and/or other factors are being randomized to receive 40 mg/day of atorvastatin or placebo for 1 year. This trial will evaluate the effect of atorvastatin on several breast cancer biomarkers, such as breast density, serum insulin-like growth factor type 1 (IGF1), and cytologic atypia and/or proliferation. The primary endpoint is to determine the effects of atorvastatin on breast density. This research is powered to detect a 3.5% difference in density.

This phase II trial will assist in determining the feasibility of larger chemoprevention studies with statins. There are

Striking activity with a novel agent was seen in *ALK*-positive NSCLC.

trial sites in California, Delaware, Massachusetts, Nevada, North Carolina, and Vermont. More information on this active study, including eligibility, may be found at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=647172&protocolsearchid=7836390&version=healthprofessional.

WEIGHT LOSS AND BREAST CANCER

Obesity and a higher percentage of body fat are considered to be risk factors for breast cancer. This pilot study investigated the effect of following a structured weight loss program to lose at least 5% of body weight on both serum and tissue breast cancer risk biomarkers (Fabian et al., 2010). The primary endpoint was the effect of weight loss on the antigen identified by monoclonal antibody Ki-67 (MKI67) level.

Postmenopausal women with a body mass index > 25 kg/m^2 who were not using hormone replacement therapy were eligible if they met risk criteria of a 5-year Gail risk > 1.7%, prior contralateral breast cancer, or precancerous biopsy and had breast tissue harvested by random periareolar fine-needle aspiration (RPFNA) indicating evidence of hyperplasia and MKI67 levels > 1.5%. However, minimum eligibility criteria were changed to cytomorphology and a frozen aliquot due to a low proportion of women with MKI67. The 6-month intervention consisted of a reduced-energy diet, physical activity, and weekly group meetings for behavioral strategies. Body composition and levels of fasting serum insulin, glucose, adiponectin, leptin, high-sensitivity C-reactive protein (CRP), interleukin-6, prolactin, sex-hormone binding globulin (SHBG), estradiol, and testosterone were assessed at baseline and post intervention.

Of the 26 evaluable patients, 20 had more than 5% weight loss; most lost more than 10% of body weight. Cytologic atypia was present in 10 of 24 patients at baseline and 4 of 24 patients at the end of the study. The median baseline MKI67 level was 0.4% and off study 0.2% for all participants and 2.2% and 0.4 % for those with baseline MKI67 levels > 1.5%.

The serum breast biomarkers that showed significant improvement included adipo-

nectin, leptin, CRP, SHBG, and estradiol (all $p < .001$). MKI67 was not a feasible endpoint of this study.

Supportive Care of Oncology Patients

Considerable research on supportive care of patients diagnosed with cancer continues. Nausea and emesis, acute pain, and cognitive problems have been well established in this patient population. Financial burden may contribute to anxiety and other physical manifestations of the disease.

INSIGHT ON FINANCIAL BURDEN

Cancer can place a significant financial burden on patients and their families. Eichholz, Pevar, & Bernthal (2010) sought better understanding of the financial issues associated with cancer and patients, caregivers, and oncology social workers.

Patients and caregivers were recruited from two national research panels, and oncology social workers were invited to complete the online survey. In all, 169 patients, 131 caregivers, and 153 oncology social workers responded.

According to the survey results, 57% indicated serious hardship related to the costs of cancer treatment, with some reporting depleted savings (40%) and bankruptcy (6%). Half of the caregivers reported trying to shield patients from the financial aspects of therapy; 73% of the oncology social workers reported discussing financial issues with all or most of their patients, and over half (58%) reported that this always or frequently had a beneficial result for the patients and caregivers. Approximately two-thirds of the oncology social workers (69%) believed that they were the patients' primary resource for dealing with these concerns.

The authors concluded that financial challenges are key issues for patients with cancer and can interfere with treatment protocols and impact adherence. Oncology social workers were identified as key individuals in supporting patients through this process, yet only one third of the patients in the study reported working with such an individual.

Oncology social workers can support patients in working through financial and psychosocial barriers to treatment.

NAUSEA AND VOMITING

Chemotherapy-induced nausea and vomiting, significant concerns for patients undergoing chemotherapy, usually are treated with a combination of a neurokinin (NK1) receptor antagonist, a steroid, and a 5-hydroxytryptamine 3 antagonist. Aprepitant (Emend) and its IV form, fosaprepitant (Emend for Injection), are the only NK1 receptor antagonists commercially available in the United States; these drugs are given as part of a 3-day regimen.

Grunberg and colleagues (2010) reported on a phase III, randomized, double-blind, active-control design study that compared use of a single dose of an NK1 receptor antagonist with the recommended 3-day regimen. Patients receiving ≥ 70 mg/m^2 of cisplatin for the first time were given the standard NK1 receptor antagonist regimen with ondansetron and dexamethasone (group A) or the study regimen of 150 mg of fosaprepitant (group F) on day 1. The primary endpoint was complete response (CR; no vomiting or use of rescue medicine during the overall period of risk [defined as 0 to 120 hours]).

A total of 1,113 evaluable patients were accrued per arm to confirm the study endpoints. Antiemetic protection was similar between both groups; the CR during the overall period of risk was 72.3% for group A and 71.9% for group F. For the delayed period (defined as 25 to 120 hours), the CR was 74.2% and 74.3%, respectively.

The researchers concluded that a single-day regimen of fosaprepitant was noninferior to a standard 3-day regimen of an NK1 receptor antagonist. However, further research concerning additional factors (e.g., serum drug exposure, timing of antiemetic administration) is needed.

COGNITIVE DIFFICULTIES

Cognitive changes associated with cancer treatment often affect the memory of patients. However, few studies on this side effect of cancer treatment have been published. Jean-Pierre et al. (2010) used a stratified, multistage probability sample of the civilian noninstitutionalized US population from the National Health and Nutrition Examina-

tion Survey (excluding patients with brain tumors) to quantify the difference in memory problems between cancer and noncancer populations.

A total of 9,819 individuals evenly matched for gender were studied; participants were ≥ 40 years of age and had diverse educational and racial or ethnic backgrounds. In all, there were 1,305 participants with cancer in the total sample and 8,514 who did not report the disease. More patients with cancer (14%) reported memory problems than did the group that did not have cancer (8%; odds ratio = 1.450; 95% CI [1.121, 1.875]). Other predictors of memory impairment included older age, gender, and poor general health ($p < .01$).

The authors concluded that having a cancer diagnosis was an independent predictor of memory impairment, which could affect quality of life. Better strategies to assess and manage this problem are needed.

Contributors: Terri S. Armstrong, PhD, ANP-BC, FAANP, Paula Anastasia, RN, MN, AOCN®, Carolyn Grande, CRNP, AOCNP®, Kristen Kreamer, CRNP, MSN, AOCN®, APRN, BC, Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP®, and Wendy H. Vogel, MSN, FNP, AOCNP®

REFERENCES

Alberts, S. R., Sargent, D. J., Smyrk, T. C., Shields, A. F., Chan, E., Goldberg, R. M., ...Nair, N. (2010). Adjuvant mFOLFOX with or without cetuximab (Cmab) in KRAS wild-type (WT) patients (PTS) with resected stage III colon cancer (CC): Results from NCCTG Intergroup Phase III Trial No147. *Journal of Clinical Oncology. 28(18s),* abstract RA3507.

Bang, Y., Kwak, E. L., Shaw, A. T., Camidge, D. R., Iafrate, A. J., Maki, R. G., ...Clark, J. W. (2010). Clinical activity of the oral ALK inhibitor, PF-02341066, in ALK-positive patients with non-small cell lung cancer. *Journal of Clinical Oncology. 28(18s),* abstract 3.

Burger, R. A., Brady, M. A., Bookman, J. L., Walker, H. D., Homesley, H. D., Fowler, J., ...Liang, X. (2010). Phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer: A Gynecologic Oncology Group study. *Journal of Clinical Oncology. 28(18s),* abstract LBA1.

Cloughesy, T., Vredenburgh, J. J., Day, B., Das, A., & Friedman, H. S., for the BRAIN Investigators. (2010). Updated safety and survival of patients with relapsed glioblastoma treated with bevacizumab in the BRAIN study. *Journal of Clinical Oncology. 28(15s),* abstract 2008.

Eichholz, M., Pevar, J., & Bernthal, C. (2010). Perspectives on the financial burden of cancer care: Concurrent surveys of patients, caregivers, and oncology social workers. *Journal of Clinical Oncology. 28(15s),* abstract 9111.

Fabian, C. J., Klemp, J. R., Kimler, B. F., Aversman, S., Phillips, T. A., Zalles, C. M., ...Yeh, H. (2010). Effect of successful weight loss program on biomarkers for breast cancer in postmenopausal high-risk women. *Journal of Clinical Oncology. 28(15s),* abstract 1522.

Grunberg, S. M., Chua, D. T., Maru, A., DeVandry, S., Boice, J. A., Hardwick, J., ...Herrstedt, J. (2010). Phase III randomized double-blind study of single-dose fosaprepitant for prevention of cisplatin-induced nausea and vomiting. *Journal of Clinical Oncology. 28(15s),* abstract 9021.

Jean-Pierre, P., Winters, P., Ahles, T., Antoni, M., Armstrong, D., Penedo, F., ...Fiscella, K. (2010). Prevalence of memory problems that limit daily functioning in adult cancer patients: A national representative sample of the U.S. population. *Journal of Clinical Oncology. 28(15s),* abstract 9134.

Malmstrom, A., Grønberg, B. H., Stupp, R., Marosi, C., Frappaz, D., Schultz, H. P., ... Henriksson, R. (2010) Glioblastoma in elderly patients: A randomized phase III trial comparing survival in patients treated with 6-week radiotherapy versus hypofractionated RT over 2 weeks versus temozolomide single-agent chemotherapy. *Journal of Clinical Oncology. 28(18s),* abstract LBA2002.

Tabernero, J., Aranda, E., Gomez, A., Massuti, B., Sastre, J., Abad, A., ... Diaz-Rubio, E. (2010). Phase III study of first-line XELOX plus bevacizumab for 6 cycles followed by XELOX plus bevacizumab or single agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: The MACRO Trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]). *Journal of Clinical Oncology. 28(15s),* abstract 3501.

Wick, W., Engel, C., Combs, S. E., Nikkah, G., Steinbach, J., Kortmann, R., ...Weller, M. (2010) NOA-08 randomized phase III trial of 1-week-on/1-week-off temozolomide versus involved-field radiotherapy in elderly (older than age 65) patients with newly diagnosed anaplastic astrocytoma or glioblastoma. *Journal of Clinical Oncology. 28(18s),* abstract LBA2001.

Wood, M. E., Kingsley, F., Ellerton, J. A., Atkins, J. N., Grubbs, S. S., Muss, H. B., Garber, J. E. (2010). A randomized trial of atorvastatin versus placebo in women at high risk for breast cancer. *Journal of Clinical Oncology. 28(18s),* abstract TPS141.