Dear colleague,

Welcome to Clinical Translations: Pearls From the 2010 Oncology Meeting. In this eCME monograph we review practice-changing findings presented at the 2010 meeting of the American Society of Clinical Oncology (ASCO) from the perspective of the community oncologist and nurse. In keeping with the meeting’s theme, we will focus on innovations in science and practice and how those advances can help us improve the quality of care we provide to our patients every day. With an increased focus on multidisciplinary cancer care and survivorship, we will explore the role of different team members in providing care, with an eye toward long-term outcomes for the individual cancer patient. We hope that you find our evaluations and distillation of clinical pearls helpful as you translate the science for your clinical practice.

Sincerely,

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Breast Cancer

Key findings in breast cancer spanned the disease state from prevention strategies to metastatic disease.

Update on Impact of HRT on Breast Cancer Outcomes

Rowan Chlebowski, of Harbor UCLA Medical Center in Torrance, California, provided an update on the results of the Women’s Health Initiative (WHI) Investigators Trial, which examined the impact of estrogen plus progesterin (E+P) supplementation on various outcomes in postmenopausal women. Previous reports from this group, based on 5.2 years of follow-up, showed that E+P use increased the risk of coronary heart disease, breast cancer, stroke, pulmonary embolus, endometrial cancer, colorectal cancer, and hip fracture. The total number of breast cancer cases was increased with E+P. Investigators also demonstrated that breast cancer was found at more advanced stages in the E+P group. In a 2009 analysis of the 5.6-year follow-up data, the increased risk of breast cancer in the E+P group decreased rapidly in about 2 years, coinciding with year-to-year reductions in combined hormone use, and this was unrelated to any change in frequency of mammography.

Until now, the WHI studies have demonstrated an impact on breast cancer incidence but not on breast cancer mortality. That end point was addressed in the current study report after a mean follow-up of 11.0 years. With the number of invasive breast cancers now at 678, the following were some of the key results of the updated analysis:

- Invasive breast cancer incidence was higher with E+P versus placebo: 385 cancers (0.42%) vs 293 cancers (0.34%); HR 1.25, 95% CI 1.07–1.46, P= .004. Baseline characteristics such as age or BMI did not affect invasive breast cancer incidence.
- Certain types of breast cancer were more common with E+P versus placebo, including HER2-overexpressed and node-positive disease.
- Breast cancer mortality was higher in the E+P vs placebo arm: 25 deaths (0.03%) vs 12 deaths (0.01%), respectively; HR 1.96, 95% CI 1.00–4.05, P=.048.
- Deaths after breast cancer diagnosis were higher in the E+P vs placebo arm: (n and % per year): 51 (0.05%) vs 41 (0.04%); HR 1.57, 95% CI 1.01–2.49 (P=.04). The authors suggest that this may be related to risk for other deaths, including lung cancer, which was increased in this cohort in a post-hoc analysis.

The authors conclude that after 11 years follow-up, 5.6 years of intervention with E+P significantly increases breast cancer incidence as well as mortality in postmenopausal women.

Clinical Implications

In his discussion of the abstract, Powel Brown, of The University of Texas M. D. Anderson Cancer Center, suggested that the increase in breast cancer incidence and mortality among E+P users is important. This is a major public health finding. He cautioned that the lung cancer data are from a post-hoc analysis. Furthermore, he suggested that the E+P effects may have been attenuated by cessation of HRT after initial reports from the study. But, he agrees with the presenter that women receiving or considering postmenopausal HRT should be counseled about the serious risks of E+P in a risk:benefit analysis.

Local/Regional Breast Cancer Therapy

Several studies examined outcomes related to various locoregional surgical and radiation therapies. Four studies are discussed below.

SLN and BM Micrometastases and Outcomes for cN0, M0 Disease

As reported by Kelly K. Hunt of The University of Texas M. D. Anderson Cancer Center, the American College of Surgeons Oncology Group (ACOSOG) study Z00107 was designed to examine the incidence and prognostic significance of occult micrometastases in women with early stage breast cancer. Occult metastases have been investigated for their prognostic and predictive value in breast cancer. A study by Cote and colleagues found that immunohistochemistry (IHC) positivity in the ipsilateral lymph node correlates with poorer disease-free survival (DFS) and overall survival (OS) in postmenopausal women with clinically and hematoxylin/eosin (H/E) node-negative disease. Braun and colleagues showed that the presence of bone marrow micrometastases at the time of breast cancer diagnosis was associated with poorer OS and progression-free survival (PFS).

In the Z0010 trial, 5210 women with clinical T1/T2, N0, M0 disease underwent breast conserving surgery with sentinel lymph node dissection (SLND) and bilateral axillary breast sampling. Women who had positive SLND results were eligible for the Z0011 study, discussed below.
Many of these patients had received systemic therapy. Of the 5210 patients enrolled, 3995 (76%) had histologically negative SNLs. Of those, 349 (10%) had IHC-positive SLN micrometastases; 104 (3.0%) of the 3413 patients who had bone marrow specimens had IHC-positive micrometastases. There was no concordance between IHC positivity (for cytokeratin) in the SLN and bone marrow. Tumor size correlated with SLN positivity but not IHC positivity in the BM.

The following were the main findings related to 5-year OS:

- H/E+ SLN: 93% vs H/E- (regardless of IHC status): 96% (P<.0009)
- Bone marrow IHC+: 90% vs IHC-: 95% (P=.01)
- Multivariate analysis
  - SLND H/E+ status: predictive of OS
    (HR 1.44, 95% CI 1.11–1.88, P=.007)
  - SLN IHC+ status NOT predictive of OS
    (HR 0.98, 95% CI 0.62–1.54, P=.93)
  - BM IHC+ status predictive of OS
    (HR 2.22, 95% CI 1.21–4.10, P=.017)

The authors conclude that this study shows excellent 5-year OS in this group of women with H/E+ SLNs. BM IHC identifies clinical T1/T2, cN0, M0 patients at significantly increased risk for death. However, IHC-detected SLN metastases do not appear to impact OS. The authors conclude that routine examination of SLND by IHC is not warranted for this population.

The Value of Axillary Dissection for SLND+, cN0, M0 Disease

Dr David Krag, of the Vermont Cancer Center, summarized the results of the NSABP Protocol B32 study, which compared SLND to SLND plus axillary lymph node dissection (ALND) in clinical T1-2 N0, M0 breast cancer. Many trials have explored the impact of ALND on survival. Orr and colleagues evaluated 6 trials that examined the impact of prophylactic ALND in women with clinically node-negative breast cancer and found a 5% survival advantage (95% CI, 2.7–8.0), although this study was conducted at a time when adjuvant therapy was not the standard of practice. In an analysis of cases from the Surveillance, Epidemiology, and End Results (SEER) database, the number of nodes removed was associated with improved survival even when all regional lymph nodes were pathologically negative, with a reduction in HR of about 5% for each additional 5 nodes removed—a difference even more pronounced in those who had positive nodes. However, ALND is not without morbidity, so a more comprehensive, modern analysis of the risk: benefit of ALND was sought. The B32 study randomized to Group 1 women with clinically negative axillary nodes (following SLND plus an immediate ALND) and to Group 2 those with ALND only for SLND positivity. This allowed follow-up in SLND-negative patients, where the only difference between the 2 groups was the application of ALND (Group 1) or its omission (Group 2).

OS analysis revealed 140 deaths in the SLND+ALND arm (n=1975), compared with 169 deaths in the SLND-only (n=2011) arm (HR =1.20, P=.117). No difference was found in DFS between the 2 groups. Local and regional recurrence was 0.1% in the SLND+ALND group compared with 0.3% in the SLND-only group. As expected, morbidity was lower and QOL was higher in the SLND-only group. The authors conclude that because there is no difference in OS, DFS, or regional control between SLND only and SLND+ALND among patients with SLND-negative disease, SLND alone with no further ALND is appropriate, safe, and effective for patients with clinically and histologically node-negative disease.

Role of Axillary Dissection in SLND+ T1-2 cN0, M0 Breast Cancer

Armando Giuliano, MD, of the John Wayne Cancer Institute, presented the results of the ACOSOG Z0011 study, which examined the role of ALND in women with clinically node-negative but SLND-positive breast cancer. According to Dr Giuliano, SLND has largely replaced ALND for lymph node staging, whereas ALND remains the gold standard for node-positive disease. However, as discussed previously, ALND carries greater morbidity than SLND. In the modern breast cancer era, tumors are smaller, the SLN is often the only positive node, the axilla is often irradiated, and patients usually receive adjuvant therapy. For these reasons, ALND may not have the substantial impact on recurrence or OS that it did in the past.

The ACOSOG Z0011 study tested the hypothesis that SLND alone achieves similar locoregional control and survival as Level I and II ALND for H/E+ SN. The study randomized women with clinical T1/T2, N0 breast cancer who underwent lumpectomy and who had H&E-detected metastasis on SLND to either ALND or no further surgery. Both groups then received whole-breast opposing tangential fields (whole breast radiation) and adjuvant systemic therapy of choice.

The study was closed early because of poor accrual. Of the 891 patients enrolled, 445 were randomized to the SLND+ALND arm and 446 to the SLND-only arm. All results are reported for the intent-to-treat sample (ITT). In the ITT analysis, T1- and ER/PR-positive cancers predominated, representing early, favorable breast cancer. Almost all patients received adjuvant therapy, either or both chemotherapy and hormonal therapy.

As expected, the median number of lymph nodes removed was higher in the SLND+ALND arm (17) vs the SLND-only arm (2; P<.001). Most invasive components of lymph nodes identified were small—37.5% in the ALND arm and 44.8% in the SLND arm were micrometastases (≤2.0 mm). Overall, 27% of patients treated with ALND had additional positive nodes beyond their SLND, yet locoregional recurrences were rare.

Recurrence rates for SLND+ALND vs SLND were as follows:

- Local breast: 3.6% vs 1.8%
- Regional: 0.5% vs 0.9%
- Total locoregional recurrence: 4.1% vs 2.8%, \( P= .11 \) at 6.3 years

Dr Giuliano suggested it is highly improbable that the 0.9% regional or 2.8% locoregional recurrence with SLND would significantly impact survival. Indeed, no difference in locoregional recurrence survival was found between the 2 groups (\( P= .25 \)). Groups that were more likely to exhibit local recurrence on multivariate analysis included those age <50 and those with high grade tumors. No difference was found in DFS between patients treated with SLND+ALND (82.2%) and those who underwent SLND alone (83.9%) (\( P= .14 \)). Similarly, there was no significant difference in OS between patients treated with SLND+ALND (91.8%) vs SLND alone (92.5%) (\( P = .25 \)). Only ER-negative status and lack of adjuvant systemic therapy were associated with reduced OS.

Dr Giuliano commented that this study shows that SLND alone provides excellent locoregional control and survival compared with completion ALND. He posits that the study does not support the routine use of ALND in early nodal metastatic breast cancer, so the role of this operation should be reconsidered.

Sentinel lymph node dissection in clinically node-negative women provides excellent locoregional control and comparable survival compared with completion axillary dissection. The role of axillary dissection in early breast cancer should be reconsidered.

Comparison of Lumpectomy + Tamoxifen +/- Radiation in Older Women

Kevin Hughes of the Massachusetts General Hospital presented data from the CALGB 9343 study on lumpectomy plus tamoxifen (tam) with or without radiation therapy (RT) in women age 70 or older with clinical stage 1, ER+ breast cancer. The study, which was opened in 1994 and closed in 1999, randomized these women to either tam+RT or tam alone to determine the importance of radiation therapy in the regimen. In total, 317 patients received tam+RT compared with 319 who received tam alone. The baseline characteristics were well balanced.

At a median follow-up of 12 years, the results showed little additional benefit following RT. Ipsilateral breast tumor recurrence occurred in 6 (2%) of the tam+RT treated patients vs 27 (9%) in the tam-alone arm (\( P = .0001 \)). However, the ultimate mastectomy rate did not differ between the 2 arms. The axillary recurrence
rate was 0 in the tam+RT arm vs 3% for the tam-alone arm. Further, the percent free of secondary primary cancer was also similar in both arms. OS rates were similar, with 157 deaths in the tam+RT arm vs 166 (33%) in the tam-alone arm (P=.9046). Similarly, the percent free from distant metastasis was similar in both arms. The authors conclude that, in older women, the benefits of RT after lumpectomy are small. One would have to irradiate 319 women to avoid 21 in-breast recurrences. Furthermore, with modern margins and use of aromatase inhibitors, RT will likely have even less benefit. However, the authors do caution that one should not apply these data to nonhormonal therapy, to ER/PR-negative tumors, or to large tumors.

Clinical Implications

In his discussion of these 4 studies of local/regional breast cancer therapy, Dr. William C Wood of Emory University commented that all 4 were consequential for practice. He noted that the Z0010 study helped establish that IHC provides no additional benefit for patients with negative SLNs. He indicated that this is consistent with the current guidelines. While the MIRROr study, which analyzed selected patients who had received NO adjuvant therapy, did show prognostic significance for IHC-positivity, the Z0010 study addresses the prognostic value of IHC positivity in the “real life” clinical situation of adjuvant therapies as actually received today. Although BM IHC positivity was associated with a difference in survival, when these data were sorted by SLN negativity, BM IHC did not have statistical significance (P=.015), so he believes it lacks clinical utility as well. Regarding the NSABP B-32 study, Dr Wood commented that the study provides definitive evidence that ALND does not provide additional benefit to SLND in clinically node-negative patients. In the review of the ACOSOG Z0011 trial, Dr Wood commented that the study restricted the analyses to patients with fewer than 3 positive SLNs and no matted nodes and that patients received radiation covering much of the axilla as well as systemic adjuvant therapy as appropriate. Nevertheless, he agreed that the study established no advantage of ALND in SLN+ patients who have fewer than 3 positive nodes and T1 disease who are undergoing breast conserving therapy, whole breast radiation, and systemic adjuvant therapy as needed.

Finally, for the study of tam +/- RT, Dr Wood notes that the study population was very specific—age 70 or older, with negative margins, tumors ≤ 2cm, cN0, with 97% ER+ or uncertain. The investigators note that irradiation, which does reduce ipsilateral breast recurrence, has no effect on ultimate breast preservation, distant metastases, or death from breast cancer or any other cause. Although Dr Wood finds these results helpful, he cautions against overextrapolating the data, since they have only been established for T1 cN0 cancers excised with clear margins in a setting of hormonal therapy.

Community Perspectives

Medical Oncology

The studies presented here identify specific groups of patients with localized breast cancer who can safely deviate from the standard of care and have less invasive or less aggressive “personalized” oncology care. Specifically, patients may be able to forgo completion ALND even in the setting of SLND+ but cN0 disease. Selected older patients with invasive breast cancer treated with lumpectomy can likely have adjuvant RT omitted. Also, it appears that lymph node analysis by IHC may be irrelevant, which is good news for medical oncologists and patients who are often faced with what seems now to be undue anxiety about how to manage nodes that are only positive based on IHC testing. Lastly, the updated WHI trial results reinforce the importance of avoiding HRT and can hopefully be effectively disseminated to primary care providers to discourage their prescribing.

Oncology Nursing

ALND remains the standard of care for patients with node-positive disease. However as a result of the SLND procedure, the number of patients who undergo ALND for staging purposes is decreasing. Based on the current data, those with clinically node-negative, microscopic disease may benefit from observation and adjuvant therapy, thus avoiding the comorbidities and long-term complications of a completion ALND such as lymphedema, neuropathies, pain, risk of infection, and quality-of-life (QOL) issues. The findings of the lack of additional benefit of adding RT to tam in select stage I breast cancer patients over age 70 represents another means to avoid unnecessary procedures and comorbidities, which is particularly beneficial in an older population. However, I agree with the discussant that these findings should not be “overextrapolated” beyond the specific study population. The medical team should discuss thoroughly the data supporting different approaches with each individual patient.

Recurrent/Metastatic Breast Cancer

Hormone-Receptor Discordance in Primary vs Recurrent Tumors

The first 2 presentations focus on discordance in pathology from the primary tumor to recurrences. Eitan Amir, MbChB, of the Princess Margaret Hospital, in Toronto, noted that literature on discordance has been garnered mainly from retrospective studies that did not reanalyze primary samples.18 Discordance may be linked to poorer survival because it can lead to inappropriate use of targeted therapies or due to selection of tumors with a higher propensity for resistance to systemic therapy.17 The current analysis set out to determine if discordance is “real” (i.e., a change in biology) or a manifestation of measurement “error” and whether the source of discordance is important.

Dr Amir summarized the pooled results of the DESTINY study, conducted at a single center in Toronto, Canada, as well as the BRITS study (a multicenter UK trial). Patients with suspected recurrence or progression were subjected to a biopsy of the recurrence, with central pathology review for ER, PR, and HER2 status. The oncologist was questioned as to the choice of therapy both before and after biopsy. The primary tissue, when available, was also reanalyzed. Discordance was defined as a change from positive to negative in receptor expression (or the reverse). Different cut-offs for this definition were used in sensitivity analyses.

The studies enrolled 271 patients, with a median age of 61. Most had hormone-sensitive tumors; 15.1% of patients had a change in therapy based on the finding of the biopsy (P<.0001). No difference was found in the likelihood of change in therapy based on a locoregional or distant recurrence. The rate of discordance was a secondary end point—38.8% of biopsies were discordant. These included both increases and decreases in receptor expression. Interestingly, some discordance was found in the re-analysis of primary tumor block as part of this study vs the pathology report from the original primary: ER 5.8%; PR 11.5%; HER2 3.8%. Exploratory analyses showed a low rate of receptor discordance in triple-negative tumors and no relationship in duration between primary and recurrence biopsy on the rate of discordance. The rebiopsy did lead to a delay in treatment (median 15 days), and 1 patient had uncontrollable bleeding from a skin punch biopsy site. Although a substantial portion of patients reported anxiety and pain with the rebiopsy, 88% reported that they would recommend a biopsy at recurrence to other patients.

The authors conclude that variability in receptor staining is well characterized. In this, the largest prospective study of receptor status in matched primary and recurrent breast cancers, the authors found substantial discordance between primaries and recurrences, most commonly in hormone receptors, less commonly with HER2, and least commonly in triple-negative disease. The authors concluded that the number needed to biopsy to alter immediate patient care was 6.6. They suggested that biopsy should be considered to confirm disease recurrence in breast cancer.

Dr Eva Karlsson of the Karolinska Institutet and Cancer Center, Karolinska, Sweden, also presented results of a study examining discordance in hormone receptor status in breast cancer during tumor recurrence/progression. Based on samples from 1095 breast cancer patients in Stockholm who relapsed between 1997 and 2007, this retrospective study compared hormonal receptor status in primary cancers and corresponding relapses. First priority was given to IHC for ER/PR, and if not available, immunocytochemistry was used from cytology aspirates.18 ER information was available from both primary and 1 or more recurrence sites in 486 patients,
resulting in 679 matched pairs. ER changed from positive to negative in 27% of these cases and from negative to positive in 8%. PR data were available in 456 patients, resulting in 630 patient pairs. PR changed from positive to negative in 38%, and from negative to positive in 5% of cases. The survival analysis showed differences based on the hormonal receptor status. The worst outcomes were in patients who were ER negative at relapse, regardless of baseline status. Upon multivariate analysis, individuals who initially had ER+ primary tumors and then had ER- tumors had a 1.5 times increased risk of death compared with ER-stable individuals (HR 1.49, 95% CI 1.04–2.11). When the analysis was restricted to patients who had systemic relapse only, those who had ER+ primary tumors who then were ER- at relapse had a nearly 2-fold increased risk of death compared with ER-stable patients (HR 1.91, 95% CI 0.20–2.84).

The investigators acknowledge that the study had limitations, including its retrospective design, the manual collection of data, and the potential for false positives and false negatives. Despite these issues, they conclude that biopsy of selected metastatic breast cancer lesions should improve the diagnostic precision to enable alternative or better therapies. In their hands, nearly every third patient changes hormone-receptor status during tumor progression, and they noted an increased risk of death among patients losing ER during tumor progression. Citing these data, multiple small and retrospective studies, as well as a prospective study examining discordance and alterations in management,19 the authors conclude that suspected metastatic breast cancer lesions should be biopsied and therapy adjusted appropriately.

**Eribulin in Heavily Pretreated Metastatic Breast Cancer**

Christopher Twelves of the Leeds (UK) Institute of Molecular Medicine presented data from the EMBRACE study of eribulin mesylate in the management of refractory metastatic breast cancer.20 Eribulin is a non-taxane microtubule dynamics inhibitor distinct from taxanes or epothilones. In a recently published phase 2 trial conducted in patients with metastatic breast cancer who had a median of 4 prior therapies, the ORR with eribulin was 11.5% (95% CI 5.7–20.1) and the clinical benefit rate was 17.2% (95% CI 10.0–26.8).21 The EMBRACE study was a global, randomized, open-label, phase 3 trial of eribulin in locally recurrent or metastatic breast cancer. The 762 patients were required to have had 2–5 prior treatments and progressed within 6 months of prior chemotherapy. They were randomized 2:1 to eribulin 1.4 mg/m², 2-5 min IV on Days 1 and 8 of each 21-day cycle. Because there is no standard of care, the physicians were permitted to select treatment (the physician choice, TPC) in the control arm, which was any monotherapy (chemotherapeutic, hormonal, or biological) and supportive care only according to guidelines or local practice.

The baseline characteristics were well balanced; the median number of prior chemotherapy regimens was 4. Approximately half of the patients had more than 2 sites of metastatic disease; the majority had liver/visceral metastases. The 1-year OS was improved in the eribulin arm (53.9%) vs the TPC arm (43.7%). The median OS was 13.12 mos in the eribulin arm vs 10.65 mos in the TPC arm—a difference of 2.47 mos (HR 0.81, 95% CI 0.66–0.99, P = .041). In the ITT analysis by independent review, median PFS was 3.7 mos for eribulin compared with 2.2 mos for TPC (HR 0.87, 95% CI 0.71–1.05, P = .14). However, PFS based on investigator review was significantly better in the eribulin arm: 3.6 mo for eribulin vs 2.2 mos for TPC (HR 0.76, 95% CI 0.64–0.90; P = .002). Of note, many more patients were censored in the independent review because they either did not have measurable disease or progressed at a site that was not measurable.

Clinical disease measures also favored eribulin. The best ORR for eribulin by independent review was 12.2% vs 4.7% for TPC (P = .002). Clinical benefit rate by independent review was 22.6% for eribulin vs 16.8% for TPC. The overall incidence of AEs was challenging to review, as the patients in the TPC arm received a range of agents. Of note, grade 3 neutropenia occurred in 21.1% of eribulin-treated patients and 14.2% of TPC-treated patients, whereas grade 4 occurred in 24.1% vs 6.9%, respectively. Grade 3 peripheral neuropathy occurred in 7.8% of eribulin and 2.0% of the TPC group.

The authors concluded the EMBRACE trial is the first phase 3, single-agent study in heavily pretreated metastatic breast cancer patients to meet an OS end point. The 2.5-month improvement in median OS is likely to be clinically meaningful in heavily pretreated patients. ORR and PFS also favored eribulin. These benefits were achieved in the context of a manageable safety profile. The authors conclude that eribulin is potentially a new option for women with heavily pretreated metastatic breast cancer.

EMBRACE is the first phase 3 single-agent study in heavily pretreated metastatic breast cancer patients to meet an OS end point.

**Clinical Implications**

Andrea Richardson of the Dana-Farber Harvard Cancer Center reviewed the studies on discordance between primary and recurrent tumors.22 She noted that the discordance rates were relatively consistent in the studies. In evaluating potential sources of error, Dr Richardson noted the differential processing of core biopsies vs breast excisions and mastectomies, the latter (which are sometimes held for several hours prior to fixation) having a deleterious effect on breast biomarkers.23,24 Similarly, fluctuation around a cutoff could be a reason for discordance—different labs use different cutoffs for defining ER positivity. In terms of plausible biologic reasons, Dr Richardson notes receptor studies are generally performed on a single block or limited core biopsies. Genomic studies show a marked heterogeneity within tumors.25 If the block misses relevant subpopulations, then discordance will result. Dr Richardson agrees with the investigators: receptor status should be routinely assessed at progression/recurrence. She anticipated that a significant number of patients will require a change in therapy based on these results.

In reviewing the eribulin data, Dr Hal Burstein, of the Dana-Farber Cancer Institute,26 noted that there is currently no standard therapy for heavily pretreated metastatic breast cancer. He commented that while there is nihilism and lack of evidence for treatments beyond 3 lines of therapy, many practitioners do continue on with therapy. Clearly there is a need for better treatments. In reviewing the results of the eribulin study, Dr Burstein noted the OS benefit but asked how such an improvement in OS could be seen in the presence of only a modest difference in PFS. From a safety perspective, he noted the higher predominance of neuropenia, febrile neutropenia, and neuropathy in the eribulin arm but considered that to be an acceptable safety profile in a heavily pretreated population. Dr Burstein raised several additional questions about the eribulin data, including outcomes in tumor subsets such as triple-negative disease, how to correct for patients who did not receive a therapeutic switch in chemotherapy in the TPC arm, how eribulin affected symptom control and QOL, and whether responders drove the survival advantage. In his final comments, Dr Burstein stated that EMBRACE provides much needed high-level evidence for outcomes in heavily pretreated metastatic breast cancer. The survival advantage is notable, but he suggested that additional studies are needed in this area and that we have a long way to go to making metastatic breast cancer a chronic disease.

**Community Perspectives**

**Medical Oncology**

Given that there are many additional agents in the arsenal for either hormone-receptor positive or HER2-positive metastatic breast cancer, it appears that confirmation of the recurrent breast cancer lesion’s receptor status is required. Assumptions that the metastatic disease has identical receptor expression as the original tumor can result in several missed opportunities to provide beneficial targeted therapies, such as trastuzumab or lapatinib, or one of several endocrine agents. With modern image-guided biopsy techniques, it is relatively safe and quick to biopsy accessible lesions. The intriguing presentation on eribulin takes us a step further towards making breast cancer a...
chronic disease. It will be exciting to follow future trial results incorporating this chemotherapy into all spectrums of breast cancer treatment. For now, it appears to be an excellent option for metastatic breast cancer treatment.

Oncology Nursing
Anxiety and fear of recurrence occurs to varying degrees in patients with cancer and may heighten as the disease progresses or as treatment becomes more aggressive. The EMBRACE trial is the first phase 3 single-agent study in heavily pretreated metastatic breast-cancer patients to meet an OS end point, offering new hope for a particularly challenging stage of the disease. By reconfirming hormone receptor status and in some cases HER2 by a simple outpatient biopsy, clinicians will be able to better determine the likely outcome of certain therapies, which could alter the course of treatment at relapse/disease progression. This could also potentially improve patient outcomes and decrease patient anxiety levels.

GYNECOLOGIC ONCOLOGY

Bevacizumab for Ovarian Cancer
Robert Burger, of the Fox Chase Cancer Center in Philadelphia, presented the results of the GOG-0218 trial of bevacizumab in the primary treatment of advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer. Vascular endothelial growth factor (VEGF)-associated tumor angiogenesis correlates with malignant behavior in ovarian cancer. Bevacizumab, a monoclonal antibody to VEGF, inhibits tumor angiogenesis and has shown impressive single-agent activity in phase 2 recurrent ovarian cancer studies.

The GOG-0218 study was a double-blind, placebo-controlled, randomized, phase 3 trial. Patients with stage III or stage IV disease were stratified according to GOG performance status and stage/debulking status, then randomized in a 1:1:1 fashion to 6 cycles of cytotoxic therapy followed by 16 cycles of maintenance. The 3 arms consisted of arm 1, the control: standard chemotherapy (IV carboplatin AUC 6 and paclitaxel 175 mg/m²) plus placebo followed by placebo maintenance (CP); arm 2: standard chemotherapy with bevacizumab 15 mg/kg followed by placebo maintenance; and arm 3: standard chemotherapy with concomitant bevacizumab followed by bevacizumab maintenance. The 1873 patients were enrolled from 336 sites. Safety was analyzed in 1816 patients, and the median duration of follow-up was 17.4 months. Baseline characteristics, age, race, PS, stage, debulking, histology, and tumor grade were balanced across the 3 arms.

Select adverse events (AEs) included Grade 2 or 3 GI events, occurring in 2.8% for arm 1, 10.3 months for arm 1 (HR 0.717, 95% CI 0.625–0.824, P<.0001).

Subset analyses showed that the benefit for arm 3 vs arm 1 was consistent across subgroups. The FDA required censoring for CA-125, and in the censored analysis the median PFS for arm 3 was 18.0 mos vs 12.0 mos for arm 1 (HR 0.645, P<.0001). At the end of the study, 77% of patients were alive. No difference in OS was found across the groups. Events had been observed in 24% of patients at the time of data lock, and unblinding to retreatment assignment was allowed at the time of disease progression.

The authors concluded that the study met its end point of improved PFS with CP+ bevacizumab followed by bevacizumab maintenance (arm 3). The treatment regimen was well tolerated, with AEs as expected and similar to previous experience with bevacizumab in metastatic nongynecologic malignancies. Bevacizumab is the first molecularly-targeted and first anti-angiogenic agent to demonstrate benefit in the front-line treatment of advanced ovarian cancer. Bevacizumab should be considered a standard option for these patients.

Clinical implications
In the review of the GOG-0218, Elisabeth Eisenhauser of Queen’s University, Kingston, Ontario, emphasized that identification of new targets such as VEGF is important for ovarian cancer. Dr. Eisenhauser acknowledged the results of the study but questioned why there was no meaningful effect in the bevacizumab-concurrent arm. She postulated that this might be related to the high response to chemotherapy in the front-line setting or to a maintenance effect only. Additional study is needed to address these questions. Dr. Eisenhauser noted that in terms of safety, no alarming findings were detected in this ovarian cancer patient population. She questioned whether the gain in PFS serves as a surrogate for survival. She quoted a 2006 analysis by FDA/ASCO/ARC that evaluated PFS as a surrogate for OS. In the analysis, the value of PFS is especially clear in first-line therapy, but the data are less clear in maintenance studies. She also suggested the importance of a cost analyses to determine the cost/year of gain, but that will require more mature data. QOL data at time of progression will also be useful as well as data from other ongoing phase 3 trials with VEGF inhibitors in ovarian cancer.

Community Perspectives

Medical Oncology
The relevance of improving PFS while not necessarily improving OS is brought into question by this study of bevacizumab in ovarian cancer. I often emphasize to my patients in incurable situations that one of our primary goals is to make sure their remaining time is as good of quality as possible. With that goal in mind and with the knowledge that active ovarian cancer often results in significant derangements in QOL, I would favor using any tolerable agent, such as bevacizumab, to improve PFS alone even if OS is not convincingly extended.

Oncology Nursing
When treating ovarian cancer patients, clinicians must be aware of the treatment AEs associated with radiotherapy, multi-modality treatment, and long duration of highly toxic treatments. QOL issues are important in all cancers but may be particularly challenging for the stage III and IV ovarian cancer patient, affecting physical, functional, social, and emotional well-being. Noting the improvement in OS with treatment in the GOG-0218 study, bevacizumab, the first molecular-targeted and antiangiogenic agent to demonstrate benefit in the treatment of advanced ovarian cancer, may improve overall QOL because of efficacy and good tolerability. We look forward to the maturation of the study data (including the presentation of the QOL data) as well as other ongoing trials with VEGF-targeted therapy.

MELANOMA

Ipiilimumab for Unresectable Melanoma
Steven O’Day, of the Angeles Clinic and Research Institute, presented data from study MDX010-20, a phase 3, randomized, double-blind study comparing monotherapy with ipilimumab vs gp100 peptide vaccine vs the combination in patients with unresectable stage III or IV melanoma. The unmet need in melanoma is large: survival rates for metastatic melanoma have remained dismal for decades. The results of this study, the first phase 3 study to show a survival benefit for a therapy used in metastatic melanoma, were recently published.

Many strategies have attempted to tweak the immune response in melanoma using various immune modulation schemes. Cytotoxic T-lymphocyte-associated antigen (CTLA-4) is an immune checkpoint molecule on the cytotoxic T cell. CTLA-4 binds to B7 on the antigen presenting cell to inhibit T-cell activation signaling. Ipiilimumab is a fully human antibody to CTLA-4 that blocks its interaction with B7, allowing immune clearance of melanoma cells. The GOG-0218 study was a phase 3 trial to show a survival benefit for a therapy in metastatic melanoma.
monoclonal antibody that blocks CTLA-4 to promote T-cell potentiation and immune responses.36 In phase 2 studies, ipilimumab showed 20% to 30% durable disease control and 2-year survival rates.36,37

The MDX010-20 study included patients with pretreated stage III or IV melanoma who were HLA-A*0201 positive. The HLA restriction was required for the gp100 vaccine, which was included in the study because it induces immune responses, and because there is currently no standard of care for metastatic melanoma. Pre-treated CNS metastases as well as any LDH level were allowed. The 676 patients enrolled were randomized to ipilimumab plus gp100 (n=403), ipilimumab plus placebo (n=137), or gp100 plus placebo (n=136). Ipilimumab was initiated at 3 mg/kg every 3 weeks x 4 doses and gp100 at 1 mg every 3 weeks x 4 doses. Reinduction with the same regimen was allowable for eligible patients.

The patient characteristics were well balanced across the study arms. As shown in the Figure, OS favored the ipilimumab-containing arms vs the gp100 monotherapy arm. The median OS in the ipilimumab + gp100 arm was 10.0 months vs 10.1 months for the ipilimumab-alone arm vs 6.4 months in the gp100 arm (HR 0.68, 95% CI 0.55-0.85 for combination vs gp100, P=0.0026). OS did not differ between the 2 ipilimumab groups. The 1-year survival rates were 44% for ipilimumab+gp100, 46% for ipilimumab, and 25% for gp100; 2-year survival rates were 22%, 24%, and 14%, respectively. The highest percentage of patients with an ORR or SD was found in the ipilimumab-alone group—an ORR rate of 10.9% and a disease control rate (OR, CR, or SD) of 28.5%. In terms of AEs, grade 3-4 immune-related AEs (IRAEs) occurred in 10%–15% of the ipilimumab group vs 3% in the gp100-alone group. Almost two thirds of ipilimumab-treated patients experienced IRAEs, which most often affected the skin and gastrointestinal tract. There were 14 deaths related to study drugs (2.1%), 7 of which were associated with IRAEs.

Dr O’Day concluded that ipilimumab represents a new class of T-cell potentiators and an important advance in the field. Further development of ipilimumab is ongoing in a variety of cancer types, in alternative combinations, and with refinements in dose and schedule.

Clinical Implications

Vernon Sondak, MD, of the H. Lee Moffitt Cancer Center in Tampa, FL, shared the excitement over the potential light at the end of the long dark tunnel in melanoma.38 Dr Sondak, reiterating the lack of progress made in treating melanoma over the last 30 years, discussed the need for a new immunologic paradigm and cited the concept of taking the brakes off the immune system with anti–CTLA-4. A vaccine may help steer that immune response, as an early study with anti–CTLA-4 and a GM-CSF vaccine model suggested.39 Overlaying the results of this MDX010-20 study on the meta-analysis conducted by Korn and colleagues,35

The ipilimumab data are being met by excitement among clinicians who care for melanoma as well as individuals diagnosed with unresectable stage III or IV melanoma. This monoclonal antibody blocks CTLA-4, promoting antitumor immunity. Although this breakthrough in ORR or documented SD is noted, one must be cautious and knowledgeable of the potential AEs such as diarrhea. Although rare, this AE can progress to GI perforation if not treated early. Further, patients may experience rash or inflammation of the skin. Management guidelines such as algorithms that include early administration of corticosteroids and close patient follow-up will significantly reduce the risk of symptom progression and decrease the occurrence of potential grade 3 or 4 AEs. Other less frequently noted side effects include hypophysitis, nephritis, and uveitis. Since the response profiles and IRAEs associated with ipilimumab represent a departure from that seen in the typical medical oncology practice, expert case discussions should be employed to help less experienced practitioners identify the range of responses occurring with ipilimumab as well as recognize critical intervention points to prevent or effectively manage IRAEs.

Oncology Nursing

Community Perspectives

Medical Oncology

Most medical oncologists have a significant level of frustration with treating intrinsically chemoresistant tumors such as melanoma. We like to have several treatment options available and like to follow algorithms that guide us in utilizing these options. To date, melanoma has not had convincingly reliable treatment options, and expert guidelines usually recommend clinical trials, which are rarely available in the community setting. That is what makes the findings of this study so exciting. We finally have a standard of care emerging that appears to have a clear advantage to patients with advanced melanoma.
HEMATOLOGIC MALIGNANCIES

Rituximab Maintenance in Follicular Lymphoma

Gilles Salles of the Centre Hospitalier Lyon Sud, in Lyon, France, presented data from the study of rituximab (R) maintenance in patients with untreated high tumor-burden follicular lymphoma (FL) after response to immunochemotherapy.10 Professor Salles explained that while the value of R maintenance has been established in relapsing patients or in the first-line setting after chemo or R, the value after R-chemo is unknown. The phase 3 Primary Rituximab and Maintenance (PRIMA) study randomized patients with stage 1, 2, or 3a FL with a high tumor burden to 1 of 3 immunochemotherapy arms: 8 cycles of R plus either 8 cycles CVP, 6 cycles CHOP, or 6 cycles of FCM. Those patients who achieved CR, CRu, or PR were randomized either to R maintenance (375 mg/m²) every 8 weeks for 2 years or to observation.

The interim analysis was stopped early after 258 events. The majority of patients had received R-CHOP as first-line therapy. Approximately 70% were in CR or CRu at the end of induction. The primary end point, PFS, was significantly improved in the R maintenance arm. At 24 months, 82% of patients who received R maintenance were progression free, compared with 66% in the observation arm (HR 0.50, 95% CI 0.39–0.64, P<.0001). The secondary end points also favored R maintenance, including time to next anti-lymphoma treatment (HR 0.61, P=.0003); time to next chemotherapy treatment (HR 0.60, P=.0011); as well as the DCR/CRu rate (66.8% with R vs 47.7% with observation).

At the end of maintenance, 95% of patients in the R arm who were in CR/CRu remained in CR/CRu, whereas only 56% did so in the observation arm; 45% of patients converted from PR/SD to CR/CRu in the R maintenance arm vs 30% in the observation arm. The AE rate was higher in the R maintenance arm, with 52% of R-maintenance–treated patients reporting any AE vs 35% in observation. Grade ≥2 infections occurred in 27% of R-maintenance–treated patients vs 22% for observation. Few patients withdrew for toxicity–related reasons.

Clinical Implications

Richard Fisher,41 of the University of Rochester, Rochester, New York, stated that the past 5 years have been a time of great advance for patients with lymphoma, with expanded immuno-chemotherapy options. Dr Fisher noted that R maintenance confers a benefit, although at the expense of some increased risk of infections. Dr Fisher asked how maintenance R compares with retreatment with R at progression. In the ECOG 4402 study, R is given up front to patients with low tumor burden, after which patients are randomized to R maintenance and R retreatment. However, it is not clear whether these data will translate to poor-feature patients. Further, Dr Fisher queried whether new induction regimens will eliminate the need for R maintenance. Dr SWOG/CALGB Trial S0016, which randomized patients to induction CHOP × 6 plus R vs CHOP × 6 + I131 tositumomab, should provide some answers. In Dr Fisher’s opinion, maintenance R is currently indicated following all treatment programs in R-sensitive patients.

Community Perspectives

Medical Oncology

This report adds to a series of prior studies all demonstrating prolonged PFS with maintenance rituximab in FL. The outstanding question as to whether patients receiving front-line treatment with rituximab benefit from maintenance treatment has now been convincingly answered. When used in this manner, this regimen appears to reduce the risk of progression by 50% without dramatically increasing the risk of AEs or impairing QOL. This strategy appears broadly applicable as a new standard of care to all patients with FL.

Oncology Nursing

FL is the most common indolent or slow-growing NHL. Most patients present with advanced-stage disease and may be offered multiple treatment options depending on symptoms, clinical presentation (ie, bulky tumor burden), and overall prognosis. The aim in treatment of FL is to maximize OS and minimize treatment-related morbidity while maintaining an improved QOL. Fear, uncertainty, dependency, depression, and anxiety typically increase at recurrence or relapse. The monoclonal antibody rituximab has been shown to be successful in reducing the risk of progression significantly while providing a reasonable safety profile. However, one must be cautious and knowledgeable about the AEs and remain vigilant in monitoring patients in the maintenance phase to avoid grade 3 and 4 AEs. Although multidisciplinary care may be challenging in some community settings, it is critical that patient education and effective clinical communication be kept up during the maintenance phase treatment of FL.

The authors conclude that R-CHOP followed by R-maintenance is a new standard of care in the management of untreated FL.

LUNG CANCER

As was the case with breast cancer, key findings across the lung cancer spectrum showed the value of appropriate staging and molecular analysis.

LN Staging Techniques

Professor Kurt Tournoy, of Ghent University, in Belgium, presented the results of a randomized trial that compared endosonography followed by surgical mediastinal staging (SS) as needed with SS alone in non-small cell lung cancer (NSCLC).42 He noted that there are currently 2 approaches to mediastinal staging: (1) SS or (2) endosonography plus needle biopsy via either esophageal approach (EUS-FNA) or endoscopic ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA).43,44

ASTER (Assessment of Surgical Staging versus Endobronchial and Endoscopic Ultrasound in Lung Cancer: A Randomized Controlled Trial) compared 2 arms: SS vs endosonography plus SS (ES+SS). The demographics were well matched across the 2 arms. Of 357 patients assessed, 241 were randomized: 118 to SS and 123 to ES+SS. Preoperative detection of nodal invasion N2/N3 differed significantly between the 2 arms, with 41 (35%) for SS vs 62 (50%) for ES+SS (P<.02). Sensitivity was 80% (95% CI 68%–89%) for SS vs 94% (95% CI 85%–98%, P=0.04) for ES+SS, with a negative predictive value of 86% vs 93%, respectively (P=.28). The futile thoracotomy rate was 18% for SS vs 7% for ES+SS (P=.009), and the complication rate was 6% for SS vs 5% for ES+SS (P=.78).

Based on these results, the authors conclude that initial endosonographic mediastinal evaluation followed by SS as needed should be the new standard of care for mediastinal staging in resectable NSCLC.

Clinical Implications

In discussing this abstract, Steven Keller of Albert Einstein College of Medicine, Bronx, NY, emphasized that staging the mediastinum is important because it provides prognostic information, helps determine study eligibility, and would support non-operative therapy for N2 disease identified prior to thoracotomy.45 In terms of whether the ASTER data prompt a change in practice, Dr Keller provided a qualified yes: the study advances our knowledge in a rigorous fashion. Concerns include the ability to obtain tissue with less invasive tests as well as the relative value of EUS. As treatment evolves, it would be important to identify patients who might not require surgical staging, to encourage pathologists to develop techniques to do molecular testing on small samples, and to support endosonography by a single clinician to reduce variability.
**Updates on Therapeutics**

### Nab-Paclitaxel

Mark Socinski of the University of North Carolina’s Lineberger Comprehensive Cancer Center, presented results of a randomized phase 3 trial of nanoparticle albumin-bound (nab) paclitaxel (nab-paclitaxel) plus carboplatin compared with cremophor-based paclitaxel and carboplatin as first-line therapy for advanced NSCLC. Dr Socinski suggests that platinum-based doublets have reached a therapeutic plateau in advanced NSCLC. Nab-paclitaxel has safety advantages over cremophor-based paclitaxel. Further, this agent makes use of the gp60/caveolin-1/SPARC transcytosis pathway to concentrate paclitaxel in the tumor. In addition, overexpression of caveolin-1 and SPARC is associated with poor prognosis in lung cancer and may provide a means of selective targeting. A phase 2 trial of nab-paclitaxel in first-line NSCLC produced an ORR of 48%, with a median OS of 11.3 mos.

The current phase 3 study randomized chemonaive patients with stage IIIb/IV NSCLC to nab-paclitaxel 100 mg/m² on Days 1, 8, and 15 and carboplatin AUC6 on Day 1 (nab-P/C, n=525) vs paclitaxel 200 mg/m² on Day 1 plus carboplatin AUC6 on Day 1 with premedication (P/C, n=525). The baseline demographics were similar in both arms. The ORR by independent radiologic review was 33% for nab-P/C (n=521) vs 25% for P/C (n=531) (rate ratio [RR] 1.31, 95% CI 1.082-1.593, P=.005). For the investigator assessment, the values were 37% vs 30%, respectively (RR 1.26, 95% CI 1.060-1.496, P=.006). Although not pre-specified, an analysis of response by histology showed an even more pronounced advantage with nab-P/C vs P/C for squamous cell histology: 41% ORR with nab-P/C vs 24% for P/C by independent review (P<.001). No difference was found between the groups among patients with nonsquamous histology. Differences were found in AEs: grade 3–4, thrombocytopenia, and anemia were more common with nab-P/C (P=.001), while neutropenia, sensory neuropathy, and myalgia were more common with P/C. Dr Socinski concluded that this randomized trial showed a significantly higher response rate for nab-P/C than P/C, an effect which was more pronounced in the squamous-cell subset.

### Oral ALK Inhibitor

Yung-Jue Bang, of Seoul National University, presented preliminary data on 82 patients for this ongoing 2-part study in ALK-positive NSCLC patients. Part 1 of the study consisted of a dose-escalation study, with 250 mg twice daily identified as the MTD/recommended phase 2 dose. Part 2 of the study is being conducted in molecularly enriched cohorts. This population differs from those typically seen in NSCLC trials in that they are younger (mean age 51), 76% never smoked, 23% were ex-smokers, and 96% had adenocarcinoma. Asians constituted 35% of the study subjects. Almost all patients had some response to crizotinib (Table). Overall, the ORR was 57% (95% CI, 46%–68%). The DCR at 8 weeks was 87%. The duration of treatment was 1 to 15 months. At the time of this presentation, the median PFS had not been reached. The PFS probability at 6 months was 73% (95% CI, 61%–83%). No grade 3–4 adverse events occurred in ≥10% of patients. The most common AEs were nausea, diarrhea, and vomiting, as well as mild visual disturbances.

The investigators conclude that treatment with crizotinib was well tolerated and provided impressive clinical activity in patients with ALK-positive advanced NSCLC. Further, these results represent an example of rapid clinical development, from target identification to clinical validation, in a personalized approach to NSCLC. Crizotinib may offer a potential new standard of care for patients with ALK-positive NSCLC. It is currently being evaluated in 2 trials in pretreated patients: the PROFILE 100877, where it is being compared with pemetrexed plus docetaxel, and PROFILE 1005, where it is being studied in the progressive disease arm of study A8081007.

### Palliative Care

Jennifer Temel of the Massachusetts General Hospital presented data supporting the incorporation of systematic symptom control and palliative care earlier in the cancer care model—at the time of diagnosis, as suggested by the Institute for Medicine in their recommendations for improving palliative care. The study randomized 150 patients with newly diagnosed metastatic NSCLC to standard oncology care or early palliative care integrated with standard oncology care. Data were collected from electronic medical records as well as relevant QOL and other scales.

The 151 patients were assigned to palliative care (n=77) or standard care (n=74), and the 12-week QOL measures significantly favored the early palliative care arm over the standard care arm:

- FACT-Lung: 91.5 (15.8 SD) vs 89.3 (17.1 SD); P=.04
- Lung Cancer Symptoms: 92.7 (3.9 SD) vs 90.5 (4.2 SD); P=.03
- Trial Outcome Index (TOI): 50.9 (11.6) vs 53.0 (11.5); P=.009

Furthermore, early palliative care significantly reduced depression, major depressive disorder, and anxiety. There were trends toward less aggressive EOL care, hospital/ER admission...
within 30 days of death, and more time in hospice in the early palliative care arm. Although not a prespecified analysis, the median survival for patients who received early palliative care was longer (11.6 months) vs that for standard care (8.9 months) (P=.02). Although the presenter recognized that this is limited to a single, tertiary site with a specialized group of clinicians, the results show impressive gains in QOL, appropriate EOL care, and survival.

Clinical Implications

In reviewing the palliative care data, Raffitt Hassari of the National Cancer Institute suggested that these data support the notion that palliative care and active cancer therapy can “go hand in hand.” He commented that nab-P/C was well tolerated and produced a higher ORR, and he looks forward to PFS and OS data. Although not incorporated in this study, he stressed the importance of incorporating biomarkers of response into future studies. In reviewing the plenary sessions on doublet-platinum therapy in the elderly, Martin Edelman of the University of Maryland Greenebaum Cancer Center observed that the data on the benefits of doublet therapy in the elderly are a departure from the recent EORTC guidelines. EORTC supports single agent therapy in the elderly, whereas the ASCO guidelines do not support selection of a specific first-line regimen based on age alone.

Community Perspectives

Medical Oncology

These presentations demonstrate that with identification of specific patient and histologic characteristics that predict for response to certain agents, the treatment of lung cancer is becoming both more tailored and more complicated. A small subset of patients with ALK-positive disease appears to have responses to crizotinib regardless of prior exposures to other chemotherapy and targeted agents. Select elderly patients who are willing and fit seem to benefit from more aggressive treatment with doublet therapy. Finally, nab-paclitaxel has the hope of benefiting squamous cell lung cancer, a subtype that has historically excluded—patients from receiving certain chemotherapy agents. The palliative care study suggests that early utilization of a palliative care team results in improved outcomes across many matrices. With the advent of palliative care specialty physicians and greater involvement of mid-level providers, this could easily become a new standard of care in patients with advanced malignancies.

Oncology Nursing

Diagnosis and staging of mediastinal masses has improved with the development of minimally invasive techniques. Mediastinal masses represent approximately 30% of thoracic tumors but staging protocols has not been consistently implemented in all practice settings. Perhaps the availability of endonsogonographic mediastinal evaluation as a first step will encourage a more proactive approach to staging while avoiding unnecessary exposure to a more invasive surgical procedure. However, the current coding and reimbursement schedules as well as training requirements may pose substantial barriers here in the United States.

Lung cancer prognosis is generally poor, but varies with tumor type and extent of disease at time of diagnosis. Therefore, potential exists for selective targeting agents as seen in patients with ALK-positive advanced NSCLC. For those with advanced or incurable disease, palliative care is recognized as an important component of QOL for cancer patients. To receive benefit, the interdisciplinary team of nursing, social services, pastoral care, along with other specialists should be engaged early on to focus on optimal treatment approaches, which may include symptom management, surgical interventions, medical and radiation therapy, as well as complementary and innovative options. Such an approach should improve QOL while maintaining realistic goals. As the palliative care team assists patients and their caregivers, we too as healthcare providers also benefit from participating in Schwartz Center Rounds, in which clinical caregivers have the opportunity to discuss their personal experiences, thoughts, and feelings in a safe, open, and relaxed environment. This forum is geared to explore the human dimension of health care while enhancing communication among caregivers with the expectation of finding life more fulfilling. Such rounds have been found helpful for caregivers, to improve communication within the health care team, and to encourage use of palliative care services.

PROSTATE CANCER

Active Surveillance

Bruce Trock, of the Brady Urologic Institute at Johns Hopkins, presented data on surgical outcomes and implications for curative in active surveillance (AS) patients who eventually undergo radical prostatectomy (RP). Surgical pathology outcomes were compared in an AS cohort who underwent delayed RP based on strict criteria vs a group of men eligible for AS but who instead chose immediate RP. In the AS program, eligible patients had a biopsy Gleason score ≤6, ≤2 positive cores, and ≤50% of biopsy core involved with tumor. Patients had an annual surveillance biopsy and semi-annual PSA, % free PSA, and digital rectal exam. Progression was defined as the point at which biopsy exceeded the above eligibility criteria (not just PSA).

As expected, the study showed significantly more patients in all AS groups (n=110) meeting the criteria for progression at time of surgery than did those in the immediate-surgery group. More patients in the AS group experienced a histologic upgrade at biopsy compared with those in the immediate-surgery arm, based on Gleason score (76% vs 22%, P=.0001) as well as nonorgan confinement (34% vs 16%, P=.002). AS not being upgraded at biopsy did not differ between the AS group and the immediate-surgery group (25% vs 22% for Gleason score and 23% vs 16% for nonorgan confinement). Thus, a missed high-grade cancer poses the greatest risk. The duration of surveillance before surgery was not associated with adverse pathology. In general, about 15% of AS men will undergo RP within 2–3 years. The rates of adverse surgical pathology are higher than in the matched immediate-surgery patients. However, Dr Trock suggests that the risk of adverse pathology represents a selection biopsy, in that higher risk is likely confined to men who were initially undergraded. The risk of adverse pathology at RP is low: for Gleason ≥ 7 it is 4.5 per 100 person years and for nonorgan confined, 1.2 per 100 person years. Regarding the controversy that AS imposes risk for those undergraded at initial biopsy, Dr Trock noted that even though recent studies show 25%-45% upgrading in immediate RP patients, most lacked a defined biopsy protocol, rigorous requirement for tumor volume on the initial core biopsies, or low PSA density. He recommends that longer follow-up and survival outcomes—along with better biomarker development—are needed to fully assess the impact of AS on outcomes.

Adding RT to ADT

Two studies evaluating the benefit of combining RT and androgen deprivation therapy (ADT) were discussed:

- Padraig Warde presented data on ADT with or without RT. Patients were randomized to continuous ADT (either bilateral orchiectomy or LHRH) or continuous ADT plus RT (45 Gy/25 F/5 weeks to pelvis; 20–24 Gy/10–12 F/2–2.5 weeks to prostate). There were 145 deaths in the ADT+RT arm and 175 deaths in the ADT monotherapy arm (HR 0.77, 95% CI 0.61–0.98, P= 0331). At 7 years, OS was 74% in the ADT+RT arm vs 66% in the ADT-only arm. Disease-specific survival favored ADT+RT (HR 0.57, 95% CI 0.37–0.78, P= .001). Late toxicities did not differ. Dr Warde proposes that ADT plus RT should be considered the standard of care for this group of patients. The optimal duration of ADT remains undefined, and the benefit of RT may be greater with dose escalation.

- Nicolas Mottet, of the Clinique Mutualiste Chirurgicale, in Saint Etienne, France, presented data on the impact of RT combined with ADT vs ADT alone for local control in clinically locally advanced PC. The
In the TROPIC study, patients with mCRPC (N=755) were randomized to CBZP 25 mg/m² q3 weeks plus prednisone for 10 courses or mitoxantrone (MP) 12 mg/m² every 3 weeks plus prednisone for 10 courses. Patients were required to have mCRPC and to have been treated with a previous docetaxel-containing regimen. Patient characteristics were well balanced across the arms, with measurable disease in over 50% of patients and visceral disease in nearly 25%. Median OS was 15.7 mos for CBZP vs 12.7 mos for MP (HR 0.72, 95% CI 0.61–0.84, P<.0001). Similarly, median PFS was longer for CBZP (2.8 mos) vs MP (1.4 mos) (HR 0.75, 95% CI 0.65–0.87, P=.0001). The ORR was 14.4 for CBZP and 4.4 for MP. In terms of AEs, neutropenia, febrile neutropenia, and diarrhea were more common with CBZP vs MP. CBZP was associated with a slightly increased risk of death due to AEs, although this was noted in Europe but not the United States. The authors conclude that CBZP, which was recently approved by the FDA, is the first treatment to show a survival benefit in patients with mCRPC after failure of docetaxel-based therapy. Although efficacy outcomes are improved, they do note that proactive management of side effects is recommended to address neutropenia and diarrhea.

Denosumab vs Zoledronic Acid for Bone Metastases

Karim Fitzai,70 of the Institut Gustave Roussy at the University of Paris, discussed the results of the study comparing denosumab with zolendronic acid (ZA) in the treatment of bone metastases in patients with CRPC. Denosumab, a fully human monoclonal antibody with high affinity for human receptor activator for nuclear factor kappa B ligand (RANKL), is delivered subcutaneously. This study was an international, randomized, double-blind study in which patients were randomized to denosumab 120 mg SC and placebo IV every 4 weeks or ZA 4 mg IV and placebo SC q4 weeks (n=951). Baseline characteristics were well balanced across the arms. More than 20% of patients in the ZA arm required dose adjustments for renal function. The time to first on-study skeletal-related event (SRE) was 20.7 mos with denosumab vs 17.1 mos for ZA (HR 0.82, 95% CI 0.71–0.95, P=.0002). The incidence of osteonecrosis of the jaw (ONJ) was low but did increase in Year 2 to 2.4% for denosumab and 0.8% for ZA. Risks for ONJ included tooth loss, dental appliance or poor oral hygiene, or chemotherapy. The authors conclude that denosumab was superior to ZA in preventing first and multiple SREs. Notable AEs included hypocalcemia and ONJ.

Clinical Implications

In discussing the active surveillance and hormonal therapy (HT) + RT abstracts for early prostate cancer, Anthony D’Amico of the Dana-Farber Cancer Institute71 reports that the ADT+RT studies show that, in general, clinical trials employing ADT + RT should receive multimodal therapy. He commented that when you add HT to RT, you get a survival benefit, but RT added to HT does not have as profound an effect on survival. In terms of strategies for the individual patient, Dr D’Amico suggests that patients with a life expectancy less than 5 years might be offered HT only, while those with a life expectancy >5 years should receive combination therapy. However, he suggests that caution should be taken in giving HT to men with congestive heart failure or MP, because the potential increases. However, level 1 evidence is needed to look at patients with comorbidities prospectively. Regarding the AS abstract, Dr D’Amico provided a holistic view, indicating that young healthy men have more to lose with disease progression or undergraded tumors with AS. He suggests the importance of incorporating comorbidities into future studies of AS. Robert Coleman, of the Weston Park Hospital, Sheffield, England72 reviewed the data supporting denosumab in mCRPC in the context of data from breast cancer and other solid tumors/myeloma. The impact on SREs is similar across the studies. From an AE perspective, he pointed to hypocalcemia and oral health that need further investigation. Several questions remain, including the impact on QOL, the duration of therapy required, and the potential of denosumab to prevent metastases. In the review of the CBZP data, Ian Tannock73 of Princess Margaret Hospital, Toronto, suggested that CBZP will become the standard of care, being the first agent to show a survival benefit in docetaxel-resistant mCRPC. However, the 4.9% death rate is a concern, and data are needed for peripheral neuropathy as well as patient-centered symptoms and QOL for this relatively toxic therapy.

Clinical pearl

Denosumab will become a new standard of care, being the first agent to show a survival benefit in docetaxel-resistant mCRPC.

Clinical Translations: Pearls from the 2010 Chicago Oncology Meeting

Complementary Perspectives

Medical Oncology

There is certainly a large percentage of newly diagnosed patients with prostate cancer that can be safely followed with close observation, but at this point it is still hard to reliably identify that patient subset. As the study presented displays, even when fairly rigid and seemingly safe parameters are in place to trigger prostate biopsy, about 50% of patients have aggressive disease at the time of resection if a close observation strategy is utilized. The studies looking at the addition of RT to ADT make it obvious that this is appropriate for fit patients with a good life expectancy. However, the lack of a clear OS advantage certainly allows for some patient and clinician discretion in choosing to add RT. The cabazitaxel data are exciting and practice changing. This agent has a definite role in progressive castration-resistant prostate cancer and seems likely to have an expanded future role once additional clinical trials are completed. Finally, the data on denosumab are consistent with prior trials showing a slight advantage over bisphosphonates in terms of SRE onset and occurrence. Since this agent appears to be safe in patients with renal insufficiency, perhaps the most exciting practical benefit of denosumab-related is that it allows for a safe, effective, and subcutaneous option for bone health in patients who had not been candidates for bisphosphonates because of renal impairment.

Oncology Nursing

These varied abstracts on prostate cancer bring to mind 2 key points—the importance of careful patient evaluation/goal assessment as well as the essential role of multidisciplinary care in prostate cancer. As emphasized by Dr D’Amico, decision-making regarding AS vs immediate prostatectomy as well as the role of ADT requires a firm understanding of patient goals and desires, life expectancy, patient comorbidities, and the potential side effects of therapies employed by urologists, radiation oncologists, and medical oncologists. Cardiovascular risk should be assessed, which may involve consultation with the primary care physician or cardiologist. With more and more elderly patients and more aggressive disease, there is further need for coordination among the team members, including the medical oncologist, the oncology nurse who manages side effects and helps educate patients, and ancillary health care providers including dentists to mitigate the risk of ONJ. Such communication/coordination can be...
facilitated by the increasing number of multidisciplinary prostate cancer tumor boards offered by health systems as well as the inclusion of Schwartz rounds, as discussed above. Further, electronic health records should be utilized to share information across practice settings and to provide reminders to disparate members of the team.

**PATIENT CARE/SURVIVOR CARE**

With an increasing focus on survivorship, there is greater emphasis on supportive care in general. Here is a brief summary of some of the key takeaways from this session.

### Spiritual/religious (S/R) Support

- **Spiritual/religious (S/R) support from the religious community actually has an unexpected effect on EOL outcomes.** This study evaluated the impact of S/R care from medical teams and religious communities on EOL outcomes. This study showed a dearth of S/R support as well as opposing effects from medical vs. religious community support. Advanced cancer patients receiving high S/R support from the medical team were nearly 3 times more likely to receive hospice (adjusted OR 2.99, 95% CI 1.45–6.17, *P* < 0.003) and were less likely to receive aggressive EOL care or to die in the ICU. The opposite was seen with S/R support from religious communities—supported patients were less likely to receive hospice care (adjusted OR 0.38, 95% CI 0.20–0.72, *P* = 0.003) and more likely to receive aggressive EOL measures or to die in the ICU. These unexpected findings suggest the need to better characterize the content/source of spiritual care and relationship to EOL outcomes as well as encourage communication between religious communities and the medical team.

- **Naproxen prevents pegfilgrastim-induced bone pain.** This study randomized 510 patients to received naproxen 500 mg twice daily or matching placebo on Days 2, 3, and 4, starting on the morning of the pegfilgrastim administration, with therapy continued for 5 to 8 days if pain continued. The AUC for pain was reduced from 7.7 in the placebo group to 6.0 in the naproxen group (*P* = 0.037). The incidence of pain was also reduced from 76.3% in the placebo group to 65.6% in the naproxen-treated group (*P* = 0.01), and the incidence of severe pain was numerically lower with naproxen vs placebo. The duration of pain was also lower in the naproxen arm: 1.92 days vs 2.40 for placebo (*P* = 0.005). Based on these results, the authors suggest that naproxen should be considered for patients beginning pegfilgrastim therapy, as long as there are no contraindications. However, the authors note the substantial proportion of patients who still experience pegfilgrastim-induced bone pain despite naproxen treatment, suggesting the need for more effective preventive treatments.

- **Denosumab is more effective than ZA in the treatment of bone metastases.** This meta-analysis pooled data from the 2 phase 3 trials in patients with metastatic bone disease from solid tumors or myeloma. Patients were randomized to denosumab 120 mg SC and placebo IV every 4 weeks (*n* = 1912) or ZA 4 mg IV and placebo SC every 4 weeks (*n* = 1910). The time to first on-study skeletal-related event (SRE) was significantly longer in the denosumab arm (not reached) than in the ZA arm (median 21.1 mos; HR 0.83, 95% CI 0.74–0.92, *P* < 0.001). The time to first subsequent on-study SRE was also prolonged in the denosumab arm (rate ratio 0.82, 95% CI 0.74–0.91). Denosumab also increased the time to first radiation to bone (HR 0.76, 95% CI 0.65–0.89, *P* < 0.001). There were no differences between the groups in overall disease progression, nor in survival. Infections/severe-infectious AE rates were similar, although acute phase reactions and renal AEs were more common with ZA. ONJ occurred in 0.5% per year in both arms. The rate of hypocalcemia was higher in the denosumab arm. These results confirm that denosumab is a potential treatment for bone metastases.

**FINAL THOUGHTS**

**Medical Oncology**

Oncology clinicians tend to get so focused on chemotherapy and its benefits on patient outcomes that we often forget the benefits of supportive care can provide. Our patients often place a higher priority on their QOL than on their quantity of life. Several studies presented here demonstrate simple non-chemotherapeutic interventions that can help with that QOL. This ASCO had several exciting presentations that have been highlighted in this monograph. Both breast and prostate cancer now have life-prolonging chemotherapy options for patients that have been heavily pre-treated. Pancreatic cancer finally has a new promising regimen for advanced disease that prolongs survival. The meeting also provided a great deal of information about how to apply less aggressive interventions to select patients with various malignancies without sacrificing outcomes. We hope this monograph on these highlighted abstracts from the 2010 ASCO annual meeting provided you with a satisfactory education and has stimulated critical thinking and dialogue on these clinically relevant presentations.

**Oncology Nursing**

As Dr Ramaekers stated, these abstracts show improvements in staging techniques as well as therapeutic advances across tumor types. While some of these advances offer ways to simplify treatment and eliminate unnecessary procedures, others require institution of newer or more complex regimes, some of which pose unique or challenging AE profiles. In general, with cancer care shifting to a more personalized and long-term approach, advances require more coordination among multidisciplinary
team members (as well as community supporters and caregivers) to provide effective, targeted therapy. Resources to help manage cancer long term include EHR with templated approaches, incorporation of care pathways, as well as patient-directed interventions such as the ASCO Cancer Treatment Summaries available for patients on the Cancer.net website. With a coordinated and integrated approach, the oncology team can continue to provide state-of-the-art, compassionate care to improve patient outcomes, including QOL.

REFERENCES


12. Giuliano AE, McCall LM, Beitsch PD, et al. ACOSOG Z0111: a randomized trial of axillary node dissection with clinical T1-2 N0 M0 breast cancer who have a positive sentinel node (SN) and bone marrow (BM) micrometastases. Presented at: American Society of Clinical Oncology Annual Meeting; June 4–8, 2010; Chicago, IL. Abstract CRA506.


with cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC). Presented at: American Society of Clinical Oncology Annual Meeting; June 4–8, 2010; Chicago, IL. Abstract LBA7511.


72. Coleman RE. The role of RANKL in castration-resistant prostate cancer. Discussion of genitourinary (prostate) cancer. Presented at: American Society of Clinical Oncology Annual Meeting; June 4–8, 2010; Chicago, IL.


