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Clinical Oncology [ALERT]

A monthly update of developments in cancer treatment and research

ABSTRACT & COMMENTARY

Single-Dose Fosaprepitant

By William B. Ershler, MD

SYNOPSIS: Current strategies to prevent chemotherapy-induced nausea and vomiting frequently include a 3-day course of aprepitant. In a multicenter trial from Japan, administration of a single dose of the aprepitant prodrug fosaprepitant, when used in combination with granisetron and dexamethasone, was shown to provide significant improvement when compared to placebo plus granisetron/dexamethasone. Thus, single-dose fosaprepitant may offer a more convenient and less complicated approach in the regimen to prevent nausea and vomiting.

SOURCE: Saito H, et al. Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausa and vomiting in patients receiving high-dose cisplatin: A multicenter, randomized, double-blind, placebo-controlled phase 3 trial. *Ann Oncol* 2013;24:1067-1073.

Chemotherapy-induced nausea and vomiting (CINV) remains a major concern for cancer patients, particularly those treated with highly emetogenic chemotherapy such as cisplatin. Traditional antiemetic agents for CINV have included serotonin 5-HT3 receptor antagonists, corticosteroids, and dopamine receptor antagonists. A more recent development has been the neurokinin-1 (NK1) receptor antagonists. The first of these to reach clinical application was aprepitant, which was shown to provide additive control on CINV in combination with existing antiemetics. However, due to formulation issues, aprepitant is only available for oral administration. Fosaprepitant, a prodrug of aprepitant, was introduced to the market in 2008 as an intravenous bioequivalent to aprepitant.

In the current report, Saito and colleagues throughout Japan evaluated the efficacy and safety of single-dose fosaprepitant in combination with intravenous granisetron and dexamethasone. The research was funded by Ona Pharmaceuticals, Osaka, Japan.

Patients treated at any of 68 participating centers who were receiving chemotherapy including cisplatin (≥ 70 mg/m^2) were considered eligible. Between August and December 2009, a total of 347 patients were enrolled. Of these, 21% had previously received cisplatin with associated vomiting. Patients previously treated with cisplatin without associated vomiting were not considered eligible. Enrolled subjects were randomized to receive the fosaprepitant regimen (fosaprepitant 150 mg, intravenous, on day 1 in combination with granisetron, 40 µg/kg, intravenous, on day 1 and dexamethasone, intravenous, on days 1-3) or the control regimen (placebo plus intravenous granisetron and dexamethasone). Aprepitant

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(the active form of fosaprepitant and a CYP3A4 inhibitor) is known to increase plasma dexamethasone concentrations when used in combination with dexamethasone (CYP3A4 substrate).[1,2] To achieve comparable plasma levels of dexamethasone in the fosaprepitant and placebo groups, the dose of dexamethasone in the fosaprepitant group was half of that in the placebo group on days 1 and 2.

The primary endpoint was the percentage of patients who had a complete response (no emesis and no need for rescue therapy) over the entire treatment course (0-120 h). The percentage of patients with a complete response was significantly higher in the fosaprepitant group than in the control group (64% vs 47%, $P = 0.0015$). The fosaprepitant regimen was more effective than the control regimen in both the acute (0-24 h post chemotherapy) phase (94% vs 81%, $P = 0.0006$) and the delayed (24-120 h post chemotherapy) phase (65% vs 49%, $P = 0.0025$).

COMMENTARY

The efficacy of the 3-day regimen of oral aprepitant in combination with ondansetron and dexamethasone has been demonstrated in a series of Phase 3 trials in patients treated with highly emetogenic chemotherapy.[3,4] There is some indication that single-dose aprepitant may be sufficient to control CINV in some patients.[5,6]

In the current multicenter trial conducted in Japan, it was demonstrated that single-dose intravenous fosaprepitant (150 mg) used in combination with granisetron and dexamethasone was well-tolerated and effective in preventing CINV in patients receiving highly emetogenic cancer chemotherapy, including high-dose cisplatin. The trial was conducted before aprepitant was approved in Japan, and thus it was not possible to determine from this work whether a single dose of fosaprepitant could substitute for the current standard of 3 days of aprepitant used in combination with ondansetron and dexamethasone. However, a subsequent Phase 3 study demonstrated comparable (i.e., non-inferior) efficacy of single-dose fosaprepitant when compared to the 3 days of aprepitant in the prevention of CINV in patients treated with highly emetogenic chemotherapy when used with ondansetron and dexamethasone.[7]

Thus, single-dose fosaprepitant is likely equally effective in preventing CINV as the 3-day course of aprepitant, and may be a less complicated and more convenient approach. Yet, there remains the one-third or more of patients who experience significant nausea and vomiting in this setting, and new drugs or treatment schedules need to be developed. ■

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ABSTRACT & COMMENTARY

Does Delaying Adjuvant Chemotherapy for Non-small Cell Lung Cancer Affect Survival?

By Gary R. Shapiro, MD
Medical Director, Cancer Center of Western Wisconsin, New Richmond, Wisconsin

Dr. Shapiro reports no financial relationships relevant to this field of study.

SYNOPSIS: One-third of non-small cell lung cancer patients treated with adjuvant chemotherapy start it more than 10 weeks after surgery. Although the time interval between surgery and initiation of adjuvant chemotherapy impacts survival in colorectal and breast cancers, delaying adjuvant chemotherapy does not appear to be associated with inferior survival in non-small cell lung cancer.

SOURCE: Booth CM, et al. Time to adjuvant chemotherapy and survival in non-small cell lung cancer. *Cancer* 2013;119:1243-1250.

This analysis, a sub-study of a population-based, retrospective cohort study of early-stage non-small cell lung cancer (NSCLC) in the Canadian province of Ontario, linked physician billing codes for chemotherapy to the Ontario Cancer Registry to describe the effect of delaying the initiation of adjuvant chemotherapy to more than 10 weeks. Although the optimal time for initiating adjuvant chemotherapy for NSCLC is unknown, the authors chose 10 weeks based on contemporary NSCLC adjuvant trials that required chemotherapy to be started no more than 8-9 weeks after surgery. In addition to cancer-related factors like histology and stage, Booth and his colleagues analyzed the role that comorbidity, socioeconomic status, age, gender, and region of residence had on overall survival (determined from date of diagnosis).

Among the 15,164 patients diagnosed with NSCLC in the province of Ontario during 2004-2006, 22% underwent surgical resection (pneumonectomy, lobectomy, or segmentectomy), of whom 31% (1032) went on to receive adjuvant chemotherapy. The median time to initiating the adjuvant chemotherapy was 8 weeks (range 1-16 weeks), and 67% of patients started within 10 weeks of surgery. Male gender, higher stage of disease, greater comorbidity, and more extensive surgery were independently associated with inferior survival. However, there was no significant difference in 4-year overall survival between patients who started adjuvant chemotherapy within 1-10 weeks after surgery and those who started 11-16 weeks after surgery (64% vs 61%, $P = 0.758$). Patients' region of residence was the only factor that was a significant predictor of delayed adjuvant chemotherapy; though male gender, higher stage of disease, greater comorbidity, and more extensive surgery were all independently associated with inferior survival.

COMMENTARY

Since it captures the overwhelming majority (98%) of all incident cases of cancer in Ontario, the Ontario Cancer Registry accurately reflects the "real life" world of community oncology. However, the authors of the current study are correct to point out that their analysis may be limited by the lack of information in the registry dealing with cancer-specific survival. Nevertheless, these are the first published data to provide insight into the optimal time of initiating adjuvant chemotherapy for NSCLC, an important contribution given the fact that one-third of patients in the Ontario population began chemotherapy more than 10 weeks after surgery.

Most oncologists like to start adjuvant chemotherapy for breast, colon, or lung cancer 3-4 weeks after surgery. They usually accept delays for up to 8-10 weeks, but hesitate to initiate adjuvant treatment beyond the 12-week mark due to lack of data regarding efficacy.

That the Ontario Cancer Registry analysis found no association between the time to starting adjuvant chemotherapy for NSCLC and survival is in marked contrast to the abundant literature dealing with breast and colon cancer that has established the importance of beginning adjuvant chemotherapy sooner rather than later. Indeed, overall survival and disease-free survival are both decreased with as little as a 4-week delay in starting postoperative adjuvant chemotherapy in patients with breast[1] and colon[2] cancer. For those with colon cancer, each 4-week delay results in a 12% increase in the risk of death.[3]

It is of course possible that the biology of NSCLC differs from that of breast and colon cancer, but a more likely explanation for this difference is the magnitude of efficacy between adjuvant chemotherapy for breast or colon cancer and NSCLC. The Booth analysis did include an assessment of the effect that the timing of adjuvant chemotherapy may have had on chemotherapy-related mortality, and found no association.

Despite its limitations, including the lack of data regarding chemotherapy delays of more than 16 weeks, this study provides important information to assist oncologists and patients as they weigh the burdens and benefits of adjuvant chemotherapy for early-stage NSCLC. Until further research is available, it provides comfort to the many patients who find themselves dealing with these questions more than 10 weeks after they have had surgery. ■

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ABSTRACT & COMMENTARY

Adjuvant Chemotherapy for Elderly Stage III Colon Cancer Patients

By William B. Ershler, MD

SYNOPSIS: In a retrospective review of adjuvant chemotherapy for elderly (≥ 75 years) patients with stage III colon cancer, performance status and comorbidities were important treatment decision factors. Disease recurrence rates were not different for those who received adjuvant treatment vs those who did not, but 1-year and 5-year survival was significantly better for the treated group. The difference at 5 years remained apparent in multivariate analysis controlling for age, performance status, and comorbidities.

SOURCE: Hoeben KWJ, et al. Treatment and complications in elderly stage III colon cancer patients in the Netherlands. *Ann Oncol* 2013;24: 974-979.

Much has been written about recognition and treatment of cancer in the elderly. This is particularly relevant because for many of the common tumors, the median age approaches 70 years or more. It is clearly understood that the elderly are not well represented in clinical trials and thus the application of evidence-based standard treatments is problematic. Such standards are often impractical based on age-associated physiological changes or, more commonly, on the existence of comorbidities, social factors (transportation, finances, etc.), or patient and family preferences. Such was the foundation for the research by Hoeben and colleagues in the Netherlands. They conducted a retrospective analysis of tumor registry data to examine factors associated with the selection of adjuvant chemotherapy for stage III colon cancer among patients 75 years and older and compared outcomes, notably, overall survival and various measures of toxicity among those who received adjuvant therapy and those who did not.

To accomplish this, population-based data from five regions included in the Netherlands Cancer Registry were used. Patients with resected stage III colon cancer aged ≥ 75 years diagnosed in 1997-2004 who received adjuvant chemotherapy (n = 216) were included as well as a random sample (n = 341) of patients who only underwent surgery.

The most common explanations for withholding adjuvant chemotherapy were a combination of high age, comorbidity, and poor performance status (PS, 43%) or refusal by the patient or family (17%). In 57% of patients receiving chemotherapy, adaptations were made in treatment regimens. Patients who received adjuvant chemotherapy developed more complications (52%) than those with surgery alone (41%).

Of the total population under analysis (517 elderly patients) who had survived at least 30 days after surgery, 211 patients (41%) developed recurrence of disease. The median time to recurrence was 420 days (4-2629 days). There was no significant difference between both treatment groups. However, for patients not receiving adjuvant chemotherapy, mortality in the first year after surgery was relatively high (33%) compared with 6% in the adjuvant treatment group. Five-year survival for the patients who had survived the first year after surgery remained significantly better for those who had received adjuvant chemotherapy (52% vs 34%, $P < 0.0001$). This effect remained significant after adjustment for differences in age, comorbidity, and PS (hazard ratio, 0.73; 95% confidence interval, 0.55-0.98). Other independent negative prognostic factors in multivariate survival analysis were advanced age (> 80 years) and extensive comorbidity.

Despite significant rates of chemotherapy-related toxicity and the frequent need for treatment schedule modifications (in approximately 50%), elderly patients who received chemotherapy seemed to have a better 1- and 5-year survival rate.

COMMENTARY

This was a descriptive, retrospective review open to a number of explanations, one of which was that the administration of adjuvant chemotherapy had beneficial effects in terms of survival. However, as the authors clearly point out, alternative explanations are also quite reasonable. Prime among these would be that patients who were relatively fit were more likely to be offered adjuvant chemotherapy. The data clearly indicated that those who did not receive adjuvant chemotherapy had a worse performance score and significantly more comorbidity. Yet, the 5-year survival remained superior for those receiving adjuvant therapy even when data were adjusted for age, comorbidity, and performance status.

The analysis included registered patients from 1997 through 2004 and thus, the great majority received 5FU-leukovorin (87%) whereas only 1% received

a combination including oxaliplatin. Data from younger patients would suggest that measures of adjuvant therapy efficacy would be improved by the inclusion of oxaliplatin,[1] but such would possibly be less well tolerated in those over 75 years.[2]

Clearly, continued clinical research including the development of appropriate assessment models for identifying those elderly patients for whom the risk/benefit ratio for adjuvant chemotherapy is favorable as well as additional prospective studies to determine optimal age-specific treatment regimens for elderly colon cancer patients is warranted. ■

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ABSTRACT & COMMENTARY

Plasma EBV Levels as a Prognostic Marker in Patients with Advanced Hodgkin Lymphoma

By Bindu Kanapuru, MD

Hematology/Oncology Division, IASIA-Falls Church, Falls Church, VA

Dr. Kanapuru reports no financial relationships relevant to this field of study.

SYNOPSIS: In this study, the authors studied the prognostic value of plasma Epstein Barr virus (EBV) DNA levels at diagnosis and 6 months post-treatment in patients with advanced Hodgkin lymphoma treated on the North American Cooperative Intergroup Trial E2496. A cutoff value of 60 copies/100 µL plasma was chosen to stratify samples as EBV(+) OR EBV(-) based on 96% concordance with tissue staining by standard viral nucleic acid (EBER) in situ hybridization (ISH). Plasma EBV positivity prior to treatment as well as at 6 months was associated with significantly shorter failure-free survival (FFS) compared to EBV negative samples. By contrast, no difference in FFS was observed when patients were stratified by EBER-ISH.

SOURCE: Kanakry JA, et al. Plasma Epstein-Barr virus DNA predicts outcome in advanced Hodgkin lymphoma: Correlative analysis from a large North American cooperative group trial. *Blood* 2013;121:3547-3553.

The gamma herpes Epstein Barr virus (EBV) has been implicated in the pathogenesis of Hodgkin lymphoma. Using standard viral nucleic acid (EBER) in situ hybridization (ISH) on tissue sections, EBV virus has been identified in varying proportions across geographic regions and age groups. In addition, EBV positivity was observed more often in mixed cellularity compared to nodular sclerosis histological sub types.[1] EBV genome is also detectable in the serum and plasma of EBV-associated Hodgkin lymphoma patients, as "naked" DNA, rather than virions and can be effectively measured in plasma using polymerase chain reaction (PCR). High degree of concordance was noted between plasma EBV DNA levels and EBER. In addition, higher EBV levels were noted in patients with advanced stage disease, older age in the presence of B-symptoms, and international prognostic score (IPS) > 2.[2]

In this study, the authors attempted to explore the relationship between plasma EBV DNA and EBV tumor status as measured by EBER-ISH and also evaluated the prognostic value of EBV DNA prior to treatment and at 6 months. There were 116 patients who had both tissue microarray specimens as well as pretreatment blood samples, and these patients were included in the 794-patient Eastern Cooperative Oncology Group–led North American Intergroup study comparing doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone). All patients had either locally advanced disease in the mediastinum or advanced (stage III or IV) histologically proven classical Hodgkin lymphoma.[3] The cutoff for plasma EBV-DNA with optimal sensitivity, specificity, and concordance with tumor EBV status by EBER-ISH was determined by a receiver operating characteristic curve and established at > 60 viral copies/100 µL for both pretreatment and 6-month samples. There was no difference between EBV(+) and EBV(-) samples and different age groups, but higher plasma EBV(+) patients were seen in mixed cellularity subtype (24% vs 9%) than nodular sclerosis subtype (43% vs 76%) and patients with higher IPS. At a plasma cutoff level of 60 copies/100 µL, failure-free survival (FFS) was inferior among those with higher EBV-DNA levels (hazard ratio, 2.0; 95% confidence interval, 1.2-3.5; $P = 0.01$). However, no difference in FFS was noted among EBER-ISH positive or negative samples. EBV(+) remained an independent prognostic factor in multivariate analysis incorporating IPS, histology, and treatment arms. Using the same cutoff value, estimated FFS at 3 years was only 48% in patients

whose samples were EBV(+) at 6 months compared to 79% in those who were negative. Median survival was not reached in patients EBV(-) at 6 months (irrespective of pretreatment EBV status) compared to 1.3 years in those who were EBV(+).

COMMENTARY

The authors have shown that pretreatment and 6 months post-treatment EBV(+) status predicts negative outcomes as evidenced by inferior FFS. The ability to identify a molecular marker that can predict clinical outcomes reliably and be easily measured is indeed an important step in the management of Hodgkin lymphoma. Current treatment for Hodgkin lymphoma includes standard radiation or chemotherapy. Several studies have attempted to stratify patients to different therapies using PET scan and clinical and laboratory prognostic scores. Recently, tumor-associated macrophages evaluated by IHC staining for CD68 and CD163 were shown to be associated with inferior FFS.[4] Increased CD68 and CD163 expression was associated with positive EBV-encoded RNA. EBV DNA measurement appears to be a unique molecular biomarker[5] that can be used to provide prognostic information and, hopefully, ultimately used as a guiding marker in developing personalized therapies for patients with Hodgkin lymphoma.

However, this study was conducted post-hoc and also included only a small sample of total patients in the study (116 of 794). Prospective testing of EBV DNA in Hodgkin lymphoma will be needed before it can be confirmed as an important biomarker for prognostic or predictive purpose. ■

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SPECIAL FEATURE

The Right Care, the Right Time, the Right Doc: Only Part of the Story…

By Robert L. Coleman, MD

Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman reports no financial relationships relevant to this field of study.

This article originally appeared in the June 2013 issue of *OB/GYN Clinical Alert*.

SYNOPSIS: Clinically significant disparities exist in the quality of ovarian cancer care delivered and in overall survival along both racial and socioeconomic status. These effects appear to persist despite adherence to National Comprehensive Cancer Network guidelines; however, deviation in guideline adherence is common and further impacts survivorship and represents key opportunities for further investigation and study.

SOURCE: Bristow RE, et al. Disparities in ovarian cancer care quality and survival according to race and socioeconomic status. *J Natl Cancer Inst* 2013 Apr 4; [Epub ahead of print].

The relationship between racial and socioeconomic status (SES) disparities and the quality of epithelial ovarian cancer care have been evaluated in previous studies but were limited by small cohort numbers and lack of a quality control benchmarks, such as guideline adherence or overall outcomes. The current population-based analysis of National Cancer Data Base (NCDB) records evaluated these factors in invasive primary epithelial ovarian cancer patients diagnosed between 1998 and 2002. Adherence to National Comprehensive Cancer Network (NCCN) guidelines was defined by stage-appropriate surgical procedures and outlined standards for adjuvant chemotherapy. The primary outcome endpoints were NCCN guideline adherence and overall survival. The context in which these outcomes were considered were race, SES, insurance payer status, household income, age, stage, histology, center where care was delivered, and education. A total of 47,160 patients (white = 43,995; black = 3165) were identified. Factors associated with inferior overall survival were non-NCCN-guideline-adherent care, black race, and Medicaid and non-insurance payer status. Tumor-specific factors, such as stage, grade, and subtype as well as hospital case volume of ovarian cancer cases, also were significantly associated with overall survival in a multilevel survival analysis. Demographic characteristics independently associated with a higher likelihood of not receiving NCCN guideline-adherent care were black race (odds ratio [OR] = 1.36, 95% confidence interval [CI] = 1.25-1.48), Medicare payer status (OR = 1.20, 95% CI = 1.12-1.28), and not insured payer status (OR = 1.33, 95% CI

= 1.19-1.49). After controlling for disease- and treatment-related variables, independent racial and SES predictors of survival were black race (hazard ratio [HR], 1.29; 95% CI, 1.22-1.36), Medicaid payer status (HR, 1.29; 95% CI, 1.20-1.38), not insured payer status (HR, 1.32; 95% CI, 1.20-1.44), and median household income < $35,000 (HR, 1.06; 95% CI, 1.02-1.11). These data highlight statistically and clinically significant disparities in the quality of ovarian cancer care and overall survival, exist independent of NCCN guideline adherence, and divide along racial and SES parameters. More work is necessary to define at-risk populations and strategies to ameliorate factors leading to these observed disparities, as well as further biological characteristics that may also impact cohort survivorship.

COMMENTARY

"Study Criticizes Care in Cancer of the Ovaries… Experienced Surgeons Can Extend Lives," was a front-page headline in the *New York Times* on March 12, 2013. The piece covered a scientific presentation made at the 2013 annual meeting of the Society of Gynecologic Oncology by gynecologic oncologist, Robert E. Bristow, MD, from the University of California, Irvine, who profiled survivorship in California ovarian cancer patients who were treated either in or out of compliance with established publically available guidelines to care. This included access to gynecologic oncologists for accurate staging and primary debulking procedures, and optimized use of effective adjuvant treatment strategies, such as dose-dense or intraperitoneal chemotherapy. The NCCN guidelines are established by a committee of disease-specific experts and generally outline sequential decision-making practices under a variety of clinical scenarios (http://www.nccn.org). Although they don't dictate practice, the guidelines provide acceptable considerations at multiple steps in care of patients. In addition, they are reported with the degree of consensus and strength of evidence-based science for these practice recommendations. Some of these algorithms are controversial, particularly when limited or poor quality data are available in the literature. However, strong consensus frequently follows level I evidence (randomized clinical trials) or from repeated historical support.[1,2] The data presented by Dr. Bristow were provocative because they demonstrated that these guidelines for ovarian cancer management were also prognostic, that is, compliance was associated with significantly better survival.

In some ways, this is not unexpected; it is clear that optimal cytoreduction (no visible residual) and use of the best chemotherapy agents, under optimal infusion schedules and modalities (all supported by positive Phase 3 trials), should provide a patient with the best that we have to offer.[3] Deviation from these approaches should (like the control arms of the Phase 3 trials) provide inferior outcomes. However, the adherence or non-adherence to guideline-directed therapy does not consider specific patient factors, underlying nuances that might add to or detract from individual therapeutic modalities, or decisions made in concert with an individual patient's desire. For example, we know that germline BRCA mutation carriers (BRCA-mt) have improved outcomes relative to those whom are BRCA-wild type (BRCA-wt).[4] However, there are differential outcomes seen within the BRCA-mt cohort relative to the modality of chemotherapy delivery. Indeed, while ovarian cancer patients appeared to have improved overall survival with intraperitoneal (IP) delivery of cisplatin and paclitaxel, the BRCA-mt patients appeared to benefit substantially better than their cohorts receiving intravenous infusion of the same agents.[5] This kind of nuance, like an audited surgical cytoreduction success variable, is not easily captured in the database from which these data were gathered. Thus, the impact, which might be only captured well by a (an unethical) trial where women were randomized to guideline-directed care vs guideline-avoided care, will not be easily sleuthed.

Added to this are the provocative results presented in the current study by the same study team. In this report, a much larger cohort of ovarian cancer patients was examined in an audited clinical database (NCDB), which reports the outcomes of about 70% of newly diagnosed cancers in the United States. They only included epithelial ovarian cancers and examined several putative prognostic factors of survival such as age, race, stage of disease, grade, payer status, median household income, education, hospital case volume, and care practices adhering to NCCN guidelines. They also looked at how these factors related to the delivery of NCCN-based care. Several striking relationships were found in the analysis. The first was that the overall 5-year survival for ovarian cancer care initiated more than a decade ago is well below 50%. Since this time, many new agents have become available; however, their widespread use is limited by lack of FDA approval and none have affected overall survival. This has greatly reduced the pace of survivorship gains over the last decade compared with the previous two. Next, putative benefit from guideline-adherent care was confirmed. Somewhat surprisingly, there was a strong relationship in survival by race stratification. Indeed, white patients faired far better than blacks in both care categories (adherent or non-adherent care). Black patients also were far less likely to get NCCN guideline-adherent care. Of interest, payer status was

strongly associated with overall survival, even when controlled for adherence to guideline care. However, black patients were significantly more likely to be classified as having no insurance/self pay or on Medicare or Medicaid, which were three of the lowest performing cohorts in outcomes among patients getting guideline-adherent care. Several factors could explain these findings, such as imbalanced degree of surgical cytoreduction, access to high-volume surgeons, intensity of chemotherapy, and different treatment strategies for management of recurrent disease. However, it also intimates that there may be intrinsic differences in patient populations, as exemplified by the data from BRCA-mt carrier status. Of interest, racial factors have been recently linked to response to novel targeted agents in other malignancies and to tolerance of chemotherapy.[6] This describes an emerging field of science called pharmacogenomics.

These data, although not definitive, are important considerations in the current climate of the Affordable Care Act. Since socioeconomic status factors have been linked to survival in ways being addressed by access to care, some of the complex issues underlying health care disparities may be engaged anew with the focus on improved outcomes to care. The expectation already has been realized in screening and prevention campaigns, where results have crossed all races and socioeconomic levels. However, much more work needs to be done on a population-based scale to understand the intricacies of how these aspects of, and to, health care can be leveraged to optimize treatment outcomes of cancer patients. ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

Continuing Education Questions

1. In the study of fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting (CINV), a single dose administered just prior to chemotherapy was shown to:

a. be equally effective in preventing CINV as a 3-day course of aprepitant.
b. be effective in preventing CINV when used as a single agent.
c. be more effective than placebo when used in combination with granisetron and dexamethasone in preventing CINV.
d. None of the above

2. Adjuvant chemotherapy for non-small cell lung cancer:

a. is just as efficacious when started 14 weeks after surgery as it is 4 weeks after surgery.
b. is usually delayed in patients with greater comorbidity.
c. All of the above
d. None of the above

3. In the report from the Netherlands regarding adjuvant chemotherapy for elderly colon cancer patients, adjuvant treatment was *not* associated with:

a. a reduced rate of disease recurrence.
b. better survival 1 year after surgery.
c. better survival 5 years after surgery.
d. None of the above.

4. In the current post-hoc analysis of the North American Cooperative Intergroup Trial E2496, the detection of EBV DNA in the plasma of Hodgkin disease patients was shown to correlate with:

a. the presence of EBV DNA within the tumor specimen as detected by in-situ hybridization.
b. shorter failure-free survival when determined prior to treatment.
c. shorter failure-free survival when determined at 6 months.
d. All of the above
e. None of the above

PHARMACOLOGY WATCH

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Do Perioperative Beta-Blockers Reduce Mortality?

In this issue: Beta-blockers and noncardiac surgery; prenatal medication exposure and risk of autism; reasons for statin discontinuations; and FDA actions.

Perioperative beta-blockers

The use of perioperative beta-blockers has been debated for decades. Now, a large study from the U.S. Department of Veterans Affairs (VA) suggests that the drugs may be of benefit in selected patients. In a retrospective cohort analysis, exposure to beta-blockers on the day of or the day following noncardiac surgery was evaluated among a population-based sample of nearly 137,000 patients from 104 VA medical centers. The main outcome was all-cause 30-day mortality and cardiac morbidity. Overall, 55,138 patients (40%) were exposed to beta-blockers, although the rate was nearly 68% in those undergoing vascular surgery. Exposure increased with increased cardiac risk factors. Death occurred in just over 1% of patients and cardiac morbidity occurred in just under 1%. Overall, exposure to beta-blockers was associated with a lower mortality (relative risk [RR] 0.73%; 95% confidence interval [CI], 0.65-0.83; $P < 0.001$; number needed to treat [NNT], 241). The effect was greater in patients with higher cardiac risk factors, which include high-risk surgery, cerebrovascular disease, ischemic heart disease, heart failure, diabetes, and renal insufficiency. When stratified by the revised Cardiac Risk Index variables, patients with two or more cardiac risk factors had a RR of 0.63 (95% CI, 0.50-0.80; $P < 0.001$; NNT, 105), with three risk factors the RR was 0.54 (95% CI, 0.39-0.73; $P < 0.001$; NNT, 41), and with four or more risk factors the RR was 0.40 (95%CI, 0.25-0.73; $P < 0.001$; NNT, 18). This effect was limited to patients undergoing nonvascular surgery. Beta-blocker exposure also significantly reduced the rate of nonfatal Q-wave infarction or cardiac arrest by 37%. The authors conclude that in patients undergoing noncardiac, nonvascular surgery, perioperative beta-blockers significantly reduced 30-day all-cause mortality in patients with two or more cardiac risk factors and support the use of the drugs in these patients. They also suggest a multicenter randomized trial to assess the benefit in patients with low-to-intermediate risk. The authors were unable to find a benefit in stroke risk or in patients undergoing vascular surgery. They were also unable to determine if various beta-blockers (such as metoprolol vs atenolol) were of benefit or if the benefit was from various dosing regimens. (*JAMA* 2013; 309:1704-1713). ■

Medication use and pregnancy

Two studies suggest that certain medications used during pregnancy may increase the risk of autism in offspring. In the first, which looked at antidepressants in pregnancy, researchers from Sweden reviewed the records of 4429 children with autism spectrum disorder (ASD) as well as 43,000 age- and sex-matched controls. A history of maternal, but not paternal, depression was associated with an increased risk of ASD and the association was confined to women reporting anti-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

depressant use during pregnancy (adjusted odds ratio 3.34; 95% CI, 1.50-7.47; $P = 0.003$). This association was irrespective of whether serotonin reuptake inhibitors or non-selective monoamine reuptake inhibitors (tricyclic antidepressants) were used. The association was confined to autism without intellectual disability. Still, the use of antidepressants accounted for only 0.6% of cases of ASD during the study, so the drugs were "unlikely to have contributed significantly towards the dramatic increased prevalence of autism spectrum disorders" (*BMJ* 2013;346:f2059). In the other study, researchers from Denmark reviewed the records of children exposed in utero to valproate (used to treat seizures and other neuropsychological disorders in mothers). Of more than 655,000 children born between 1996 and 2006, 5437 identified with ASD, including 2067 with childhood autism. The overall risk of autism in all children was 1.53%, but of the 508 children exposed to valproate, the absolute risk was 4.42% (95% CI, 2.59-7.46%) for ASD and 2.50% (95%CI, 1.30-4.81%) for childhood autism (adjusted hazard ratio, 5.2). The risk was similar regardless of the indication for use of valproate in the mother. These findings suggest that maternal use of valproate significantly increases the risk for ASD and childhood autism in offspring. The authors suggest that a risk-benefit analysis should be considered for women on valproate in their childbearing years (*JAMA* 2013;309:1696-1703). ■

Discontinuation of statins

Most patients who stop statins due to side effects will tolerate the drugs if rechallenged, according to the findings of a new study. In a retrospective cohort study using data from two Boston hospitals, researchers reviewed the records of nearly 108,000 patients on statins and found statin-related events such as muscle pain documented in 18,778 (17.4%). Of those patients, 11,124 stopped the drugs at least temporarily and 6579 were restarted within the subsequent 12 months. The vast majority of patients restarted on a statin tolerated the drug (92.2%), although about half were eventually switched to a different statin. The authors conclude that statin-related side effects are common and often lead to discontinuation; however, most patients who are rechallenged can tolerate statins long-term. They suggest that "statin-related events may have other causes, are tolerable, or may be specific to individual statins rather than the entire drug class" (*Ann Intern Med* 2013;158:526-534). ■

FDA actions

The FDA has updated labeling of the new tamper-proof oxycodone (OxyContin), while at the same time denying approval of generic forms of the original formulation of oxycodone. The new labeling indicates that the product "has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)." The agency's refusal to approve generic forms of the original formulation was based on the increased risk of abuse inherent in the non-tamper proof form leading to the risk of serious adverse events including overdose and death. Because of this, the agency has determined that the benefits of the original OxyContin and its generics no longer outweigh its risks and it has been withdrawn from sales. The new tamper-proof formulation is more difficult to crush, break, or dissolve. If tampered with, it forms a viscous hydrogel that cannot be easily injected or snorted. Oral abuse is still possible.

The FDA has approved a fixed combination of doxylamine succinate and pyridoxine for the treatment of nausea and vomiting due to pregnancy. This is a reintroduction of a product widely used between 1956 and 1983. Then marketed as Bendectin, the product was voluntarily withdrawn by the manufacturer due to lawsuits related to birth defects, although evidence of risk was not supported by scientific evidence. The reapproval was based on a study of 261 women experiencing nausea and vomiting due to pregnancy in which the drug was more effective than placebo in relieving symptoms. Since the 1980s, observational studies have shown that doxylamine and pyridoxine do not pose an increased risk of harm to the fetus. The recommended starting dose is two tablets taken at bedtime on an empty stomach. The combination is marketed by Duchesnay Inc. as Diclegis.

The FDA has approved prothrombin complex concentrate for the rapid reversal of anticoagulation by warfarin and other vitamin K antagonists. Plasma is the only other option for this use currently available, and prothrombin complex can be given at significantly lower volume than plasma. The product is made from pooled plasma of healthy donors that is processed to minimize the risk of viral and other diseases. The approval was based on a study of 216 patients who were anticoagulated and had major bleeding. Plasma complex concentrate was found to be similar to plasma in its ability to stop major bleeding. Plasma complex concentrate is marketed by CSL Behring as Kcentra. ■

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By Louis Kuritzky, MD

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Risks and Benefits of an Extended 10-year Tamoxifen Regimen for Breast Cancer

Source: Davies C, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of estrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-816.

The prevailing 5-year tamoxifen regimen for breast cancer has been shown to reduce breast cancer mortality by as much as one-third over a 15-year interval; a comparison with a shorter regimen (1-2 year) found the longer duration to be superior. Would even longer tamoxifen administration (i.e., > 5 years) provide even greater risk reduction of breast cancer and its consequences, and if so, would longer regimens induce greater toxicity to other non-targeted tissues (e.g., induction of endometrial cancer)?

The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial randomized women with estrogen receptor-positive breast cancer (B-CA) to either 5 years (n = 3418) or 10 years (n = 3428) of tamoxifen. Follow-up continued for 5 years after conclusion of the 10-year tamoxifen course. The estrogen-receptor positive B-CA group actually represents only about half of all of the women enrolled in ATLAS; the estrogen-receptor negative population of ATLAS demonstrated no risk reduction through longer tamoxifen administration.

Numerous outcomes favored 10-year tamoxifen over 5 years and were statistically significant: B-CA recurrence (617 vs 711 cases), B-CA mortality (639 vs 722 deaths), and ischemic heart disease death or hospitalization (127 vs 163 cases). On the negative side of the equation, all-cause mortality was not impacted by the longer tamoxifen regimen, and there was a significant increase in pulmonary embolism (41 vs 21 cases) as well as endometrial cancers (116 cases vs 63 cases).

These results were apparently sufficiently impressive enough to make the cover story in the *Lancet*. Your reviewer, however, takes pause at the fact that — similar to the situation with results for prostate cancer screening, which has recently been diminished by convincing evidence that screening may reduce prostate cancer mortality but not total mortality — a 10-year tamoxifen regimen reduces B-CA mortality but not total mortality, and has not-insubstantial adverse effects as well as costs. ■

Is There More Pro than Con in Probiotics in Critically Ill Adults?

Source: Barraud D, et al. Impact of the administration of probiotics on mortality in critically ill adult patients. *Chest* 2013; 143:646-655.

The technical definition of probiotic offered by the World Health Organization and the Food and Agriculture Organization sounds promising enough: "viable microorganisms that, when ingested in a sufficient amount, can be beneficial for health." Unfortunately, the existing literature on the benefits of probiotics is not quite so convincing.

Barraud et al performed a meta-analysis of randomized, controlled trials published between 1950-2012 in which probiotics were used in the intensive care unit (ICU) setting, ultimately netting 13 clinical trials, all published after 2002 (n = 1439). The probiotic used in each of these trials was in the *Lactobacillus* family, and although some trials used only one *Lactobacillus* strain, several trials used mixed strains of *Lactobacilli*. Endpoints included ICU mortality, hospital mortality, ICU infections, incidence of diarrhea, and duration of mechanical ventilation.

Of the above-mentioned endpoints, a statistically significant favorable odds ratio was seen only for the incidence of ICU-acquired pneumonia, even though the overall larger category of ICU-acquired infections was not statistically significantly improved. Although the failure to achieve significance to numerous endpoints is disconcerting, the authors point out that since probiotic administration is generally safe, the favorable impact on ICU-acquired pneumonia (a reduction of approximately 40%) might prompt consideration for use in patients known to be particularly at risk for this consequence. ■

Are OSA Outcomes Better in the Hands of Sleep Specialists than Primary Care Clinicians?

Source: Chai-Coetzer CL, et al. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: A randomized trial. *JAMA* 2013;309:997-1004.

The recognition of obstructive sleep apnea (OSA) as a health burden of compelling epidemiologic presence with significant impact on both quality of life

and cardiovascular health has been recognized by health care providers of essentially all disciplines. Increasingly, sophisticated sleep laboratory monitoring devices allow ever more detailed (and usually more costly) understanding of sleep dysregulation. At the same time, awareness of the frequency and consequences of OSA among diverse disciplines of medicine has resulted in a sufficiently burgeoning population of individuals who merit screening that sleep labs are often unable to keep pace with the increasing demand.

A proliferation of simpler, home-based tools for the identification and potential management of OSA that can be used by sleep specialists and primary care clinicians alike has prompted the question of whether outcomes for OSA patients attended by sleep specialists (who are usually not primary care clinicians), typically with complex sleep analysis tools (which are most commonly employed in a specific sleep laboratory), are superior to outcomes for patients attended by primary care clinicians with less sophisticated home-based tools.

The authors report on a randomized, controlled, non-inferiority trial of patients with OSA identified and treated either in a university sleep laboratory by sleep specialists or by community primary care practices. The primary outcome was improvement in the Epworth Sleepiness Scale, a commonly used and validated scoring system for monitoring sleepiness associated with OSA.

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At the end of the 6-month trial, scores on the Epworth Sleepiness Scales were identical in both groups, and outcomes in the primary care group were determined to be non-inferior to sleep specialist care. Hopefully, primary care clinicians will become more involved in the identification and management of OSA, since equally salutary outcomes are seen in their hands as in the hands of sleep specialists. ■

Inhaled Steroids Increase Risk of TB in COPD Patients

Source: Kim J, et al. Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. *Chest* 2013; 143:1018-1024.

Reactivation of tuberculosis (TB) is an ongoing concern among patients who receive immunosuppressive agents such as TNF-alpha agents for rheumatoid arthritis. Similarly, long-term use of systemic steroids (i.e., ≥ 30 days) in amounts as small as 7.5 mg/day of prednisone increases the risk of TB. Inhaled corticosteroids (ICS) have been associated with systemic effects such as growth retardation (in asthma), reduced bone mineral density, and increased risk of pneumonia (in chronic obstructive pulmonary disease [COPD]). Whether ICS might also be associated with risk for development or reactivation of TB has not been fully clarified.

Kim et al performed a retrospective analysis of COPD patients (n = 620) in a university hospital in South Korea (where the background prevalence of TB is substantially greater than many other nations) to compare the rate of TB activation in persons who had received ICS with controls. To eliminate the confounding factor of systemic steroid use, COPD patients who had received ≥ 7.5 mg for 1 month or more were excluded from the analysis.

There was a substantially greater and statistically significant risk for development of active TB among COPD patients who had been treated with ICS (hazard ratio = 9). In patients whose baseline chest x-ray showed evidence of prior (but quiescent) TB, the hazard ratio for activation of TB was 25!

Although the prevalence of TB is much greater in Korea than in the United States, these data suggest greater vigilance for TB activation in patients chronically using ICS, especially if their x-rays indicate evidence of prior TB. ■

The ASH Position Paper on Orthostatic Hypotension

Source: Shibao C, et al. ASH position paper: Evaluation and treatment of orthostatic hypotension. *J Clin Hypertens* 2013;15:147-153.

Standing from a seated or supine position is normally associated with minimal, if any, blood pressure (BP) change, thanks to homeostatic mechanisms that alter splanchnic and peripheral blood compartments by selective intravascular redistribution and vascular tone. When BP change upon standing exceeds 20/10 mmHg, a diagnosis of orthostatic hypotension (OH) is established. Although tilt-table testing is often suggested for formal diagnosis, simple office measurement of BP 1-3 minutes after standing suffices.

Although sometimes OH produces minor distracting symptoms of dizziness that may be diminished by standing slowly, leg crossing, maintenance of good fluid balance, etc., it can also be a cause of falls, with anticipatable subsequent catastrophes such as hip fracture. Additionally, OH epidemiological data have noted an association between OH and stroke.

A variety of commonly used medications can precipitate or exacerbate OH, including alpha blockers, diuretics, vasodilators, dopamine agonists, and tricyclic antidepressants, modulation of which may OH improve symptoms. Pharmacologic treatments for OH include fludrocortisone (to increase intravascular volume), midodrine (a short-acting vasopressor agent), and other sympathomimetic agents.

OH is also seen in several primary neurologic disorders such as Parkinson's disease, multiple system atrophy, and Lewy body dementia.

Clinicians should suspect OH particularly in patients who report dizziness, unexplained falls, or syncope, although even symptoms such as blurred vision or neck/shoulder pain ("coat hanger" distribution pain) may reflect OH. Fortunately, a variety of lifestyle and pharmacologic treatments can be helpful. ■