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ABSTRACT & COMMENTARY

Bone Mineral Density after Oophorectomy and Tamoxifen in Premenopausal Breast Cancer

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

SYNOPSIS: In a study conducted as an adjunct to a randomized, Phase 3 investigation of optimal timing of oophorectomy for premenopausal breast cancer patients, Love and colleagues examined changes in bone mineral density (BMD) for patients receiving surgery (oophorectomy and mastectomy) plus tamoxifen. They observed a decline in lumbar spine BMD at a rate that lessened over 2 years, and no significant change in BMD at the femoral neck. The implications of this finding relate to the optimal management of premenopausal breast cancer, particularly in countries with limited health care resources.

SOURCE: Love RR, et al. Bone mineral density following surgical oophorectomy and tamoxifen adjuvant therapy for breast cancer. *Cancer* 2013;119:3746-3752.

In premenopausal patients with hormone receptor-positive breast cancer, adjuvant ovarian ablation plus tamoxifen therapy has been shown to improve overall survival.[1,2] A recent meta-analysis revealed an overall clinical trend toward ovarian ablation over hormonal treatment with luteinizing hormone-releasing hormone (LHRH).[2] However, loss of ovarian function, and the subsequent menopausal state, is associated with loss of bone mineral density (BMD) and increase risk of fracture.[3] In postmenopausal women with breast cancer, tamoxifen has been shown to preserve BMD.[4,5] However, previous studies have demonstrated a loss of BMD in premenopausal women with breast cancer treated with tamoxifen alone.[5] Additional studies have demonstrated loss of BMD in patients treated with LHRH agonists plus tamoxifen.[6,7] However, to date, no studies have investigated the effect of oophorectomy plus tamoxifen on BMD in premenopausal women with breast cancer.

To evaluate the effect of surgical oophorectomy on BMD in premenopausal women with hormone receptor-positive breast cancer, Love and colleagues conducted a longitudinal ancillary study of women participating in a Phase 3 clinical trial investigating the timing of surgical oophorectomy. Initially, 740 Vietnamese and Filipino premenopausal women with hormone receptor-positive invasive breast cancer

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were enrolled in the parent Phase 3 trial. In this trial, patients were initially stratified based on likelihood of being in the luteal phase of the menstrual cycle. Patients in stratum 1 (not in the luteal phase) were randomized to either immediate surgical oophorectomy or delayed surgical oophorectomy during the estimated mid-luteal phase of the menstrual cycle. Patients in stratum 2 (in luteal phase) underwent immediate surgical oophorectomy. All patients underwent surgical oophorectomy and mastectomy on the same day, and all were started on tamoxifen 20 mg daily within 6 days of surgery.

The inclusion criteria for the parent study were as follows: age ≥ 18 years and ≤ 50 years, history of menstrual cycles for the last 3 months with a duration of 25-35 days each, last menstrual period < 35 days ago, no current oral contraceptive use, histologic diagnosis of invasive and hormone receptor-positive (estrogen receptor-positive and/or progesterone receptor-positive) breast cancer with clinical stage II-IIIB, no other underlying serious illnesses, negative chest x-ray, and negative urine pregnancy test.

Because this ancillary study was initiated late and several sites did not participate, BMD data on 270 patients (175 in stratum 1 and 90 in stratum 2) were available for analysis. BMD was evaluated in the lumbar spine (L1-L4) and the femoral neck at the time of study enrollment and randomization (baseline). All patients had between 1 and 3 follow-up evaluations, using the same equipment, within the first 30 months of treatment.

The average age of study participants was 42.7 years (SD 4.3), weight was 54.3 kg (SD 11.3), and body mass index (BMI) was 23.1 (SD 3.7). Of the 270 participants, 64.6% were diagnosed with stage I-II disease and 35.5% had stage III disease.

A non-linear regression model was used to assess changes in BMD over time. Significant changes were observed for lumbar spine BMD post-intervention. At 6 months, BMD had declined by 2.8% (95% confidence interval [CI], -3.5 to -2.1; $P < 0.0001$). At 12 months, BMD had declined by 4.7% (95% CI, -5.5 to -3.8; $P < 0.0001$), and at 24 months BMD had declined by 6.7% (95% CI, -7.7 to -5.6; $P < 0.0001$). However, there were no statistically significant changes in femoral neck BMD.

Data were also analyzed with respect to patient age, weight, and BMI. Patients ≥ 43 years of age had an average of 0.030 g/cm^2 lower baseline femoral neck BMD than those < 43 years of age. However, the rate of decrease in BMD post-intervention was the same in both age groups. There was no difference in baseline lumbar spine BMD between the age groups. There were no significant changes in the rate of decline of BMD based on weight or BMI.

COMMENTARY

In this analysis, which represents the largest of its type examining BMD changes in premenopausal patients receiving adjuvant therapy, there was clearly defined evidence that surgical oophorectomy followed by immediate tamoxifen treatment was associated with loss of BMD at the lumbar spine, the rate of which declines over 2 years but, curiously, no significant change in BMD at the femoral neck.

These findings are particularly relevant to the management of hormone receptor-positive premenopausal breast cancer in countries where, for economic reasons, adjuvant treatment might not include expensive chemotherapy regimens such as those including taxanes and ancillary agents such as bisphosphonates or denosumab. Prior studies have shown surgical oophorectomy plus tamoxifen to be superior to LHRH plus tamoxifen and to be equivalent with chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil plus LHRH plus tamoxifen. Thus, the comparable lumbar spine BMD losses and absence of BMD loss in the femoral neck would speak in favor of oophorectomy and tamoxifen as the optimal adjuvant approach, with equivalency in breast cancer management and less dramatic negative consequences in terms of bone loss. ■

References

1. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 2005;365:1687-1717.
2. Love RR, et al. *J Clin Oncol* 2008;26:253-257.
3. Siris ES, et al. *Arch Int Med* 2004;164:1108-1112.
4. Love RR, et al. *N Engl J Med* 1992;326:852-856.
5. Powles TJ, et al. *J Clin Oncol* 1996;14:78-84.
6. Sverrisdottir A, et al. *J Clin Oncol* 2004;22:3694-3699.
7. Shapiro CL, et al. *J Clin Oncol* 2001;19:3306-3311.

ABSTRACT & COMMENTARY

Comparison of Two Chemotherapy Regimens for Malignant Pleural Mesothelioma

By William B. Ershler, MD

SYNOPSIS: In a randomized, Phase 2 trial conducted in Egypt comparing gemcitabine/cisplatin vs pemetrexed/carboplatin for the primary treatment of malignant pleural mesothelioma, the latter resulted in a slightly improved response rate and less toxicity but no significant difference in survival.

SOURCE: Habib EE, Fahmy ES. Chemotherapy management of malignant pleural mesothelioma: A phase II study comparing two popular chemotherapy regimens. *Clin Transl Oncol* 2013;15:965-968.

The incidence of malignant pleural mesothelioma (MPM) is increasing worldwide and the prognosis remains poor. Currently, the standard of care involves a multimodal approach including chemotherapy, surgery, and radiation. Evidence has suggested that single-agent chemotherapy is not sufficient, as no single drug has been shown to have a beneficial response in > 20% of patients.[1,2] However, of the single chemotherapy agents tested, a meta-analysis revealed that cisplatin is the most active, with a response rate of 13-14%.[2,3] Recently, a Phase 2 trial showed activity of the anti-fol pemetrexed in patients with MPM.[4] A Phase 2 trial of combination therapy with pemetrexed and cisplatin compared to cisplatin alone demonstrated significant improvements in response rates in those who received both drugs (41.3% vs 16.7%, $P < 0.0001$), as well as in median survival (12.1 months vs 9.3 months, $P = 0.020$).[5] As a result, this combination of pemetrexed and cisplatin has been established as the standard of care for MPM. However, because of its lower toxicity profile, carboplatin is often selected as the preferred platinum agent, and when combined with pemetrexed, it produced comparable results in terms of MPM disease response and overall survival.[6]

Habib and colleagues conducted a prospective, Phase 2 clinical trial to investigate the effectiveness of two different chemotherapy regimens, gemcitabine and cisplatin vs pemetrexed and carboplatin, in patients with non-resectable MPM. Forty patients with histologically proven untreated MPM were enrolled at a single institution in Egypt from May 2008 through May 2011 and were blindly randomized to one of two treatment groups. Twenty-one patients were randomized to Group 1 and received six cycles of cisplatin 80 mg/m^2 on day 1 and gemcitabine 1 g/m^2 on days 1, 8, and 15. Nineteen patients were randomized to Group 2 and received six cycles of pemetrexed 500 mg/m^2 on day 1 and carboplatin at an AUC of 5 mg/mL/min on day 1. All patients received folic acid and vitamin B12 supplementation with the aim of decreasing toxicity. The only significant differences between the patients in the two groups were age and gender. The mean age of the patients in this cisplatin group was 62.2 years (SD ± 8.9 years) vs 49.5 years (SD ± 11.7 years) in the pemetrexed group ($P < 0.001$). There were 19 males and 2 females in the cisplatin group and 10 males and 9 females in the pemetrexed group ($P = 0.012$).

Patient evaluations included a medical history, physical examination, and laboratory studies at baseline and prior to each cycle of chemotherapy. Chest x-rays were done monthly, and CT scans of the chest and abdomen were done at baseline and every 3-6 months after treatment completion, depending on symptoms or other clinical indications. Response was determined based upon assessment of clinical symptoms and radiographic data. The median follow-up was 18 months (range 6-30 months).

Overall toxicity (grades 1-4) appeared to be worse in patients who received the cisplatin regimen. Specifically, more patients experienced thrombocytopenia (66.6% vs 26.3%, $P = 0.014$), nausea/vomiting (100% vs 5.3%, $P < 0.001$), diarrhea (47.6% vs 0.0%, $P = 0.001$), and hearing loss (42.9% vs 5.3%, $P = 0.001$).

Of the 19 patients in the pemetrexed treatment group, one had a complete response (CR), 14 had a partial response (PR), three had progressive disease (PD), and one had stable disease (SD). Of the 21 patients in the cisplatin treatment group, there were no patients who had a CR, 10 had a PR, two had PD, and nine had SD. Overall response rate (CR + PR) was superior in the pemetrexed treatment group vs the cisplatin group (78.9% vs 47.6%, respectively, $P = 0.041$). Overall survival at 1.5 years appeared to be better for patients treated with pemetrexed (57.8% vs 41%). However, this difference was not statistically significant ($P = 0.0599$).

COMMENTARY

Thus, the combination of pemetrexed and carboplatin was demonstrably active for patients

with MPM, comparable in response rate and less toxic than cisplatin/gemcitabine. Although responses were better than those reported for single-agent treatment, there remains much need for improvement. ■

References

1. Ong ST, Vogelzang NJ. *J Clin Oncol* 1996;14:1007-1017.
2. Zidar BL, et al. *Inves New Drugs* 1998;6:223-226.
3. Berghmans T, et al. *Lung Cancer* 2002;38:111-121.
4. Hazarika M, et al. *Clin Cancer Res* 2005;11:982-992.
5. Vogelzang NJ, et al. *J Clin Oncol* 2003;21:2636-2644.
6. Ceresoli GL, et al. *J Clin Oncol* 2006;24:1443-1448.

ABSTRACT & COMMENTARY

Treatment of ALL in the Elderly

By William B. Ershler, MD

SYNOPSIS: Experience treating acute lymphoblastic leukemia in the elderly using pediatric full-dose regimens has met with high rates of toxicity and induction-related mortality. Recognizing this, Martell and colleagues at the Princess Margaret Hospital in Toronto modified the standard pediatric-based protocol to reduce anticipated toxicity. Analysis of 51 patients treated on the modified regimen was associated with an excellent complete remission rate (75%) and overall survival at 5 years. Yet, induction-related mortality remained high at 20%. Thus, the modified protocol represents a step forward but further adjustments will be required to optimize treatment outcomes.

SOURCE: Martell MP, et al. Treatment of elderly patients with acute lymphoblastic leukemia using a pediatric based protocol. *Br J Haematol* 2013;163:458-464.

Much has been written about the treatment of acute myelogenous leukemia in the elderly but considerably less about acute lymphoblastic leukemia (ALL). Yet, approximately 30% of all ALL occurs in adults over the age of 60 years,[1] and the treatment successes documented for younger patients has not resulted in enhanced survival for this subset.[2-4] It has been speculated that a higher frequency of comorbidities and impaired functional status often limit dose, appropriate scheduling, or even utilization at all of effective chemotherapy. Furthermore, established ALL adverse prognostic factors have been demonstrably worse in elderly patients.[3,4]

Improved outcomes in younger adult ALL patients have been largely attributed to the widespread adoption of pediatric-based protocols, including intensification of certain drugs such as corticosteroids, vinca alkaloids, and asparaginase, and adhering strictly to the treatment schedule. The applicability of such intense protocols has been questioned for older patients in light of anticipated toxicity. For example, Brandwein and colleagues reporting the 11-year experience in treating ALL in those ≥ 60 years at the Princess Margaret Hospital found a 56% complete remission (CR) rate with 27% induction-related mortality rate in those receiving multiagent chemotherapy.[5] Further, the median overall survival was 9 months, while the median progression-free survival (PFS) for those achieving CR was 10 months. These authors concluded that aggressive induction regimens designed for younger patients proved very toxic in the elderly and suggested the investigation of less aggressive regimens in older patients.

In the current report, this group at the Princess Margaret Hospital now retrospectively report their experience with a modified-for-age protocol for older patients. Over a 7-year period, all newly diagnosed ALL patients aged 60-79 years received induction chemotherapy with a dose- and drug-adjusted pediatric-based regimen (n = 51, median age 65 years). As with the standard pediatric protocol (DFCI 91-01), the treatment regimen consisted of induction, central nervous system prophylaxis, seven cycles of intensification, and 24 cycles of maintenance. However, the standard protocol was modified by substituting pulse dexamethasone for daily prednisone, reducing methotrexate dose from 4 g/m^2 to 40 mg/m^2, reducing asparaginase dose from 25,000 IU/m^2 to 12,000 IU/m^2, and removing one vincristine dose. BCR-ABL positive patients were given imatinib 400 mg daily for 16 days instead of asparaginase. In the CNS prophylaxis phase, cranial radiation was removed. In the intensification phase, seven cycles were given instead of 10, the cumulative dexamethasone dose was reduced by approximately 75%, and the cumulative asparaginase dose reduced by 66%, compared to the full regimen. In the maintenance phase, parenteral methotrexate was switched to oral, and the dexamethasone dose was reduced from 6 mg/m^2 to 6 mg. For patients who developed progressive grade ≥ 2 neuropathy, intravenous vinblastine 10 mg was substituted for vincristine. For patients with low left ventricular ejection fraction, amsacrine 75 mg/m^2 was substituted for doxorubicin.

The complete response rate was 75%, with an induction mortality of 20%; 6% of patients had resistant disease. Thirty-seven percent of patients who

achieved a complete remission relapsed. The estimated 5-year overall survival was 40% for BCR-ABL negative and 47% for BCR-ABL positive patients; the 5-year disease-free survival was 57% and 39%, respectively (P = NS). The post-induction phase was generally well tolerated, with 81% able to complete the intensification phase and proceed to maintenance.

COMMENTARY

This report on the treatment of older adults with ALL is of great interest and represents a step forward in achieving optimal management for this subset of patients. The prior application of the more aggressive DFCI or comparable regimens resulted in unacceptable induction-related mortality rates and relatively low survival numbers as detailed in their prior report.[5] The modified protocol, using basically the same metrics, proved significantly better, including a CR rate of 75% and an estimated disease-free survival at 5 years of 40% and 47% for BCR-ABL negative and positive patients, respectively. Yet, induction mortality remained quite high (20%), indicating a continued need for exploration of treatment regimens, particularly during the early phase.

The patients included in the current report had been referred to the Princess Margaret Hospital for treatment and the authors mention that only two otherwise eligible patients were excluded because of comorbidities. There is concern that the study population may not reflect typical elderly ALL patients, many of whom are not referred to academic centers but are treated in the community. Thus, the current report may help guide ALL treatment for otherwise well elderly, but there remains much to be learned on optimal management for those more frail. This will become increasingly relevant as older patients tend to be managed in the community rather than referred to academic centers, and the numbers of such patients are expanding dramatically. ■

References

1. Taylor PR, et al. *Blood* 1992;80:1813-1817.
2. Pagano L, et al. *Leuk Lymphoma* 2004;45:117-123.
3. Sancho JM, et al. *Eur J Haematol* 2007;78:102-110.
4. Sive JI, et al. *Br J Haematol* 2012;157:463-471.
5. Brandwein JM, et al. *Leuk Res* 2005;29:1381-1386.

ABSTRACT & COMMENTARY

Cetuximab-Gemcitabine for Cholangiocarcinoma: The Belgian Experience

By William B. Ershler, MD

SYNOPSIS: In a multicenter Phase 2 trial, cetuximab combined with gemcitabine resulted in a progression-free survival rate of 47% at 6 months and median overall survival of 13.5 months. KRAS mutation status did not predict enhanced progression-free survival but the occurrence of grade 3/4 skin toxicity did.

SOURCE: Borbath I, et al, on behalf of the Belgian Group of Digestive Oncology. Combination of gemcitabine and cetuximab in patients with advanced cholangiocarcinoma: A phase II study of the Belgian Group of Digestive Oncology. *Ann Oncol* 2013;24:2824-2829.

Cholangiocarcinomas occur uncommonly and remain without effective treatment. The tumors arise from the neoplastic transformation of biliary epithelial cells either within the liver or extrahepatic biliary ducts, most commonly at the hilum.[1,2] In part because of their relatively uncommon occurrence, advances in treatment have been slow in development. Thus, surgery remains the only chance for long-term survival, and radical approaches, such as hepatic transplantation, have been undertaken under selected circumstances.[3,4] For patients with unresectable disease, some improvement in progression-free and overall survival has been achieved with gemcitabine and cisplatin systemic therapy.[5] The demonstration of overexpression of the epidermal growth factor receptor (EGFR) in some cases of cholangiocarcinoma[6] or mutated forms in others[7] has led to the speculation that EGFR might be an effective target for treatment of cholangiocarcinoma.

Accordingly, the Belgian Group of Digestive Oncology reports a multicenter Phase 2 trial in chemotherapy-naive patients with unresectable cholangiocarcinoma using the monoclonal EGFR-blocking antibody cetuximab (400 mg/m^2 at week 1, then 250 mg/m^2/week) and gemcitabine (1 g/m^2 on days 1, 8, and 15) every 4 weeks. The primary endpoint was progression-free survival (PFS) rate at 6 months, using a Simon 2-stage design. Secondary outcomes included overall survival (OS) and safety profile. Further, the PFS and OS results were examined in the context of skin toxicity and KRAS mutational status.

Enrolled patients either had locally advanced disease (41%) or demonstrable metastatic disease (59%).

Median age was 61.5 years and performance status (ECOG) was 0 (68%) or 1 (32%). Six-month PFS reached 47%. Median OS was 13.5 months (95% confidence interval [CI], 9.8–31.8 months). Nine patients (20.4%) had PR and disease-control rate was 79.5%. Grade 3/4-related toxic effects were hematological (52.2%), skin rash (13.6%), and fatigue (11.4%). KRAS mutations were found in 7 of 27 patients and had no influence on PFS. Skin toxic effect ≥ grade 2 was associated with increased PFS ($P = 0.05$).

COMMENTARY

The authors conclude that gemcitabine and cetuximab is an active combination for patients with cholangiocarcinoma, as PFS exceeded what would be expected for gemcitabine alone.[8] In the small sample size, KRAS mutation status offered no predictive value in contrast to treatment-related skin toxicity, which was a statistically significant indicator of improved PFS.

An alternative to the cetuximab-gemcitabine combination would be cisplatin-gemcitabine. In 2010, the Upper Gastrointestinal Cancer Clinical Studies Group of the United Kingdom published results from the ABC-02 trial in which 410 patients (including those with cholangiocarcinoma as well as gall bladder and ampullary cancers) received either cisplatin (25 mg/m^2) followed by gemcitabine (1000 mg/m^2), each administered on days 1 and 8, every 3 weeks for eight cycles, or gemcitabine alone (1000 mg/m^2 on days 1, 8, and 15, every 4 weeks for six cycles) for up to 24 weeks.[5] Median survival was 11.7 months for those receiving both drugs compared to 8.1 months for those receiving gemcitabine alone. PFS also favored the combination (8.0 months vs 5.0 months, respectively). Thus, the combination (cisplatin/gemcitabine) would seem comparable to cetuximab/gemcitabine as currently reported. However, the Belgian and U.K. studies were different in many important ways, particularly with regard to inclusion criteria warranting caution with regard to such a comparison.

What is fair to conclude is that cetuximab combined with gemcitabine is an active regimen to be considered for patients with unresectable or metastatic cholangiocarcinoma. A direct comparison with the cisplatin/gemcitabine regimen in a randomized trial might establish one combination as superior in terms of both efficacy and tolerability. Short of that, clinicians may rely on these published reports and their own experience to select first-line systemic therapy in this setting. ■

References

1. Gores GJ. *Hepatology* 2003;37:961-969.
2. Nakeeb A, et al. *Ann Surg* 1996;224:463-473; discussion 473-475.
3. Heimbach JK, et al. *Semin Liver Dis* 2004;24:201-207.
4. Jarnagin WR, et al. *Ann Surg* 2001;234:507-517; discussion 517-519.
5. Valle J, et al. *N Engl J Med* 2010;362:1273-1281.
6. Hezel AF, et al. *J Clin Oncol* 2010;28:3531-3540.
7. Leone F, et al. *Clin Cancer Res* 2006;12:1680-1685.
8. Andre T, et al. *Ann Oncol* 2004;15:1339-1343.

SPECIAL FEATURE

Cancer Survivorship…The Marriage Effect?

By Robert L. Coleman, MD

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

This article appeared in the November 2013 issue of OB/GYN Clinical Alert.

SYNOPSIS: Compared to cancer patients who were never married, divorced, widowed, or separated, married patients are significantly more likely to present at an earlier stage, undergo therapy with definitive or curative intent, and live longer among each of the 10 most common cancers killers in the United States. The data suggest the effect is rooted in better social support mechanisms among this cohort and highlight a modifiable "at-risk" population.

SOURCE: Aizer AA, et al. Marital status and survival in patients with cancer. *J Clin Oncol* 2013; Sep 23. 10.1200/JCO.2013.51.5080 [Epub ahead of print].

The positive effect of marriage on cancer survivorship previously has been reported but is not universal among various investigations.[1,2] The authors set out to examine the impact of marital status on stage at diagnosis, use of definitive therapy, and cancer-specific mortality between each of the 10 leading causes of cancer-related death in the United States. To interrogate a sample large enough to adjust for the various covariates, they identified more than 1.2 million cancer patients registered in the Surveillance, Epidemiology and End Results (SEER) program diagnosed between 2004 and 2008. Ten primary tumor sites (lung, colorectal,

breast, pancreatic, prostate, liver/intrahepatic bile duct, non-Hodgkin lymphoma, head/neck, ovarian, or esophageal cancer) were addressed, as they represented the most common diagnoses associated with cancer-specific morality. After eliminating cases with inadequate clinical and follow-up information, 734,889 patients were available for analysis. The authors found that married patients were less likely to present with metastatic disease (adjusted odds ratio [OR], 0.83; 95% confidence interval [CI], 0.82-0.84; $P < 0.001$), more likely to receive definitive therapy (adjusted OR, 1.53; 95% CI, 1.51-1.56; $P < 0.001$), and less likely to die as a result of their cancer after adjusting for demographics, stage, and treatment (adjusted hazard ratio, 0.80; 95% CI, 0.79-0.81; $P < 0.001$) than unmarried patients. These associations remained significant when each individual cancer was analyzed ($P < 0.05$ for all endpoints for each malignancy) and regardless of unmarried status ($P < 0.001$ for each unmarried category). The benefit associated with marriage was greater in males than females for all outcome measures analyzed ($P < 0.001$ in all cases). For prostate, breast, colorectal, esophageal, and head/neck cancers, the survival benefit associated with marriage was larger than the published survival benefit of chemotherapy. The authors concluded that unmarried patients are at significantly higher risk of presentation with metastatic cancer, undertreatment, and death resulting from their cancer, even after adjusting for known confounders. This study highlights the potentially significant impact that social support can have on cancer detection, treatment, and survival.

COMMENTARY

"My wife says I never listen to her…at least I think that's what she says…."

The impact of marriage on survivorship in cancer patients has been extensively examined in previous reports, but with inconclusive independent results. Most have shown a benefit but have been confounded by small samples size for individual malignancies, regionality, lack of information regarding follow-up, and survival not linked to cancer-specific events. However, the current study's design and analysis, while not optimal (e.g., a randomized trial), does provide some confidence the association is credible. This comes from several considerations. First, the sample was based on cancer-specific survivorship, that is, those cases in which death was recorded as a cancer event. This type of analysis censors patients who die before progression or from causes not related to cancer. In treatment trials, this endpoint is often considered to be biased because elderly patients are more likely to die of intercurrent disease leading to extensive censoring. However, for the current analysis, it provides cleaner data to assess the effect of the variable (marriage at diagnosis) on cause-specific outcomes across a variety of tumors. The second aspect affording credibility to this study's hypothesis-generating suppositions is the multi-regional patient inclusion. The SEER database captures more than 95% of the incident cancers from registries representing more than a quarter of the U.S. population. There are well-documented deficiencies in this database (e.g., no pathology review, lack of information regarding chemotherapy, oversimplified, and lack of confirmation of staging), but the demographics, diagnoses, stage category, some treatment, and outcomes recorded have been continually validated and updated for years. Third, the sample is large enough to consider important covariates such as, age, race, gender, residence, income, education, tumor and nodal stage, and treatment. In the context of marriage, these are important variables since married cancer patients tend to be younger, have higher incomes and education level, may have broader and better access to health care, and live in rural homesteads with larger family support mechanisms.[3] Considering these factors, marriage was still significantly protective and remained so against the 10 tumor types examined and relative to each unmarried category. Further, the effect in many tumor types (prostate, breast, colorectal, esophageal, and head/neck) was stronger than the impact of chemotherapy.

The primary takeaway message from this article, and others on the topic, is that marriage provides a critical internal social support system that is less often present among patients who are unmarried — these patients represent a risk group that deserves attention. While the quality of marriage among those married and the contribution of live-in unmarried cohabiters could not be directly assessed, it appears the marriage at the time of diagnosis is associated with important primary treatment variables that would be expected to result in better outcomes. For instance, most primary outcome measures, such as overall survival, progression-free survival, and objective response, are directly associated with tumor stage at presentation; earlier stage = better outcomes. Thus, tumors in which symptomatology may be reflective of an early-stage diagnosis (e.g., epistaxis in head and neck cancer) are more likely to be associated with better outcomes if a partner encourages ("nagging") a doctor's appointment at first occurrence.[4] Earlier stage at presentation would also increase the likelihood of definitive treatment options and increase the odds of finishing a prescribed treatment plan. Each of these factors

has been broadly associated with more favorable survival in a variety of cancers. In ovarian cancer, symptomatology is not associated with earlier stage at presentation, but may be associated with lower metastatic tumor burden, affording a higher likelihood to undergo primary surgical debulking, to have a better cytoreduction outcome, and complete definitive adjuvant therapy. Finally, chronic stress has been implicated as negatively impacting cancer survivorship, particularly in regard to immune function and the tumor microenvironment, where stress is associated with accelerated angiogenesis and immune escape.[5,6] The hypothesis that married patients are less likely to suffer chronic stress and depression than their unmarried counterparts has been previously raised and may contribute to the study's findings.

So how can this information be leveraged? The knowledge that unmarried cancer patients represent an at-risk group provides an opportunity to develop and evaluate social support mechanisms that can act as surrogates for a live-in partner. Most cancer centers have regular patient supportive-expressive group therapy sessions. However, their impact on survival has been mixed in the few randomized controlled studies that have been conducted.[7,8] Nevertheless, comprehensive programs that provide not only social-expressive opportunities but also assessment/management of depression and anxiety and assistance with decision making represent the best opportunity to close the "survival gap" observed in unmarried individuals. Increased awareness and assessment of depression/anxiety should be afforded to all cancer patients. However, knowing the risks that may further impact and complicate a patient's treatment program, clinicians are encouraged to thoroughly evaluate the social support structure of unmarried patients at presentation and during their follow-up. ■

References

1. Nelles JL, et al. *Urol Oncol* 2009;27:263-267.
2. Goodwin JS, et al. *JAMA* 1987;258:3125-3130.
3. Ayanian JZ, et al. *N Engl J Med* 1993;329:326-331.
4. Aizer AA, et al. *J Clin Oncol* 2012;30:3071-3076.
5. Sephton SE, et al. *Brain Behav Immun* 2013; 30(Suppl):S163-S170.
6. Sephton SE, et al. *J Natl Cancer Inst* 2000;92:994-1000.
7. Spiegel D, et al. *Cancer* 2007;110:1130-1138.
8. Temel JS, et al. *N Engl J Med* 2010;363:733-742.

Continuing Education Questions

1. In examining bone mineral density in premenopausal, hormone receptor positive breast cancer conducted in Vietnam and the Philippines, Love and colleagues found that oophorectomy resulted in significant loss in bone mineral density at which site?
a. Lumbar spine
b. Femoral neck
c. Both a and b
d. Neither a nor b

2. The combination of pemetrexed and carboplatin when compared to gemcitabine with cisplatin in the treatment of malignant pleural mesothelioma resulted in:
a. fewer objective antitumor responses.
b. better overall survival.
c. better overall tolerability.
d. None of the above

3. The modified acute lymphoblastic leukemia (ALL) protocol applied to elderly ALL patients, when compared to earlier experience with full-dose, pediatric-based ALL protocols demonstrated improvement in all but which of the following?
a. Complete remission rate
b. Induction-related mortality
c. Overall survival at 5 years
d. Disease-free survival at 5 years

4. In the Belgian multicenter trial of gemcitabine plus cetuximab for patients with cholangiocarcinoma, which of the following predicted improved progression-free survival?
a. KRAS mutation status
b. Treatment-related skin toxicity
c. Both a and b
d. Neither a nor b

5. Marriage was associated with a stronger effect on overall survival than chemotherapy in which of the following cancers?
a. Ovarian
b. Liver
c. Pancreatic
d. Lung
e. Colorectal

Clinical Oncology [ALERT]
Evidence-based summaries on cancer treatment and research

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Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Goldilocks Unable to Find Amount of Antioxidants That's Just Right

Source: Bjelakovic G, et al. *JAMA* 2013; 310:1178-1179.

The observation that excess oxidative stress is associated with diverse pathologic consequence has been consistently coupled with the obvious next intellectual step: antioxidants *should* be beneficial to prevent these consequences. Unfortunately, no Goldiloks has stepped forward to inform us which antioxidant is too much, which is too little, and which is just right. Or maybe the antioxidant hypothesis is just a fairy tale, after all?

This is not the first time that observational hypotheses have disappointed. In two clinical trials of antioxidant supplementation in persons at risk for lung cancer (combined n > 45,000), the first trial found an *increase* in lung cancer and mortality, and the follow-up trial was discontinued almost 2 years early because of similar outcomes.

This most recent Cochrane systematic review included 78 trials (n = 296,707) performed in both primary and secondary prevention modes. The "bottom line" is worth quoting: "Antioxidant supplements are not associated with lower all-cause mortality. Beta carotene, vitamin E, and higher doses of vitamin A may be associated with *higher* all-cause mortality." Some naysayers would suggest that we have not yet fulfilled the Goldilocks systematic approach: Maybe we used too little, maybe we used too much, or maybe we used the wrong formation, and have not yet found the approach that's "just right." For now, the science does not support a role for antioxidants in primary or secondary prevention. ■

Antipsychotics Are Associated with Increased VTE Risk

Source: Wu CS, et al. *J Clin Psychiatry* 2013;74:918-924.

Antipsychotics have suffered a beleaguered course of late: literature showing little efficacy advantage of newer vs older agents, concerns about increased mortality associated with their use, etc. A recent report suggests that antipsychotic treatment is also associated with a clinically meaningful increase in risk for venous thromboembolism (VTE), comprised of deep vein thrombosis plus pulmonary embolism.

Wu et al performed a case-control study of enrollees in the National Health Insurance Research Database of Taiwan to compare cases of confirmed VTE (n = 2162) with age-matched controls without VTE (n = 12,966). Initial analysis looked simply at the relative risk of antipsychotic use in persons with VTE vs controls. Second-step analysis adjusted for confounders.

Overall, the adjusted odds ratio for VTE in current antipsychotic users was 1.52 (i.e., current users were 52% more likely to experience VTE than controls); the odds ratio was substantially worse (3.26: a more than 3-fold increase in risk) for new users. These concerning results were attained even after correction for confounding factors such as utilization of thrombogenic medications (e.g., oral contraceptives) and medical comorbidities associated with increased VTE risk (e.g., congestive heart failure). Analysis of different classes of antipsychotics did not find any particular distinction among them. The mechanism by which antipsychotics might increase VTE risk is uncertain, although the authors posit that antipsychotic-induced sedation could lead to less physical activity with subsequent venous stasis. In any case, these data suggest vigilance for VTE in persons prescribed antipsychotics, especially in the early months of use. ■

Physician Visits for Itching

Source: Shive M, et al. *J Am Acad Dermatol* 2013;69:550-556.

If results from the National Ambulatory Medical Care Survey conducted by the CDC are correct, pruritus as a presenting complaint in ambulatory care may merit more of our attention. In a retrospective review of data from 1999-2009, there were approximately 7 million office visits per year in which pruritus (or itching) was indicated as a presenting symptom. In comparison, there were almost 18 million visits per year for low back pain. Since itch may or may not have been specifically indicated when syndromes such as a drug allergic reaction occur, the authors suggest that these numbers likely *underestimate* the true prevalence of pruritus.

The consequences of pruritus may range from minor nuisance to intolerable. Indeed, patients taking opioid analgesia frequently mention pruritus as a treatment-limiting adverse effect. Fortunately, clinicians have a diversity of agents to treat pruritus, including multiple generations of antihistamines as well as steroids (topical and systemic). Finally, it has been

recognized for more than 2 decades that doxepin — traditionally used as an antidepressant — has antihistaminic potency as much as 50 times greater than the most potent "traditional" antihistamines such as hydroxyzine. Because of this antihistaminic potency, doxepin is often used in refractory urticaria, when other antihistamines have failed, even though sedation is common at typical therapeutic doses. ■

Consequences of Non-Adherence in Treated Hypertensives

Source: Cummings DM, et al. *J Am Soc Hypertens* 2013;7:363-369.

The relationship between elevated blood pressure (BP) and stroke is linear and continuous. An abundance of clinical trial data indicate that treatment of hypertension (HTN) by means of numerous diverse classes of antihypertensives lowers stroke risk by ≥ 40%. Clinical trials, however, are not "real life." The Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study is examining a large population (n = 30,239) of southeastern men and women with HTN. Their assessment of the relationship between self-reported degree of antihypertensive medication adherence and serious outcomes (stroke/TIA) from a subset population (n = 15,071) is quite sobering.

During a 5-year window of observation, study participants were grouped into four categories of adherence using the Morisky scale, which translates into general groupings of high, good, moderate, and low adherence. Perhaps not surprisingly, mean systolic BP in the high adherence group was substantially better than the low adherence group (131 mmHg vs 138 mmHg). Incidence of stroke or TIA was 8% higher in the lowest adherence group compared to the highest. Good BP control has meaningful payoff; every decrement of adherence less than that is costly. ■

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Long-Term Risk-Reduction Benefits of Sigmoidoscopy and Colonoscopy

Source: Nishihara R, et al. *N Engl J Med* 2013;369:1095-1105.

Participants from two large observational studies provide an opportunity to evaluate the risk reduction accrued from either colonoscopy (COL) or sigmoidoscopy (SIG). The Nurses' Health Study (n = 121,700 female nurses) and the Health Professionals Follow-up Study (n = 51,529 male health professionals) have more than 20 years' prospective follow-up of their participants. During this interval, there were 1185 cases of colon cancer and 474 deaths from colon cancer.

Skeptics have long held fast to the tenet that SIG had an advantage over COL: proven risk reduction for colon cancer mortality for the former. Although the intuitive additional advantage of examining the entire colon with COL seemed a no-brainer, purists argued that whether COL was truly better than SIG was not yet proven, and that since COL was associated with greater risks (perforation, adverse effects from sedation, etc.), there was reasonable basis to continue with SIG as a preferred method. In accord with this philosophy, noting the many missed opportunities for colon cancer screening and prevention, advocacy groups rallied around the call-to-action, "The best colon cancer screening test is whichever one you can get done!"

These data may change that perspective, since the risk reduction for colon cancer death was almost twice as great for COL as SIG (hazard ratios, 0.59 vs 0.32). The "no-brainer" part of the equation was also resoundingly confirmed: COL reduced mortality from proximal colon cancer by more than half compared to no risk reduction through SIG. ■

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Warfarin Outperforms Dabigatran in Patients with Mechanical Heart Valves

Source: Eikelboom JW, et al. *N Engl J Med* 2013;369:1206-1214.

The atrial fibrillation (AF) headlines have been filled with celebration over the efficacy of factor Xa inhibitors (e.g., rivaroxaban, apixaban) and direct thrombin inhibitors (e.g., dabigatran) for prevention of thrombotic events. Since warfarin — though highly effective, exhaustively studied, and time-tested — also has distinct clinical burdens (e.g., need for monitoring, food interactions, drug interactions), agents that were at least as efficacious for thrombotic risk reduction — with fewer of these same clinical burdens — were welcomed.

Success in AF, however, does not necessarily translate into other pathologies. Eikelboom et al studied patients with recent mitral or aortic mechanical valve replacement (n = 252). Subjects were randomized to dabigatran or warfarin. About one-fourth of these patients also had AF.

The trial had to be discontinued early because of untoward events in the dabigatran group: stroke occurred in 5% of the dabigatran group vs none in the warfarin group, and major bleeding was twice as common on dabigatran (4% vs 2%). Although earlier trials in animals were encouraging, these data indicate that warfarin is safer and better tolerated in patients with recent surgery for prosthetic mechanical heart valves. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Reglan Safe in Pregnant Women for Nausea and Vomiting

In this issue: Reglan safe in pregnancy; battle brewing over naming of biosimilar drugs; and FDA actions.

Reglan safe in pregnancy

Use of the anti-nausea medication metoclopramide (Reglan) in pregnancy is not associated with an increased risk of major congenital malformations, spontaneous abortion, or stillbirth. These were the findings of large, register-based cohort study from Denmark. The safety of metoclopramide in pregnancy has been of concern because it is increasingly used to treat pregnant women with nausea and vomiting. Metoclopramide-exposed pregnant women were matched with unexposed women in a 1:4 ratio, with more than 40,000 exposed women in the cohort, of whom more than 28,000 received the drug in the first trimester. The drug was not associated with major malformations or any of more than 20 individual malformations. There was no increase in spontaneous abortion, stillbirth, preterm birth, low birth weight, or fetal growth restriction (*JAMA* 2013; 310:1601-1611). ■

Battle over naming of biosimilar drugs

A battle is shaping up between biotech companies and the Generic Pharmaceutical Association (GPhA) over the naming of biosimilar drugs. Biosimilars, or "follow-on biologics," are products whose active ingredient is an approved version of a previously approved biopharmaceutical. Since biologics are generally manufactured in a complex process that may include molecular clones and proprietary cell lines, it is virtually impossible for the manufacturers of a biosimilar to match the process step-by-step. This results in small differences between the innovator product and the follow-on product (hence the name "biosimilar"). With billions of dollars of revenue at stake, biotech companies, such as Genentech and Amgen, have been lobbying federal and state legislators to tighten the rules regarding use of biosimilars. There has also been concern that the FDA might prohibit biosimilar manufacturers from using the same generic name as the original drug, a move that biotech companies would endorse and the GPhA would strongly oppose. A bipartisan group of senators recently entered the fray by penning a letter to the FDA urging the agency to allow biosimilars to share the name of the innovator product. Led by Republican John McCain and Democrats John Rockefeller and Tom Harkin, six senators urged the FDA to follow the intent of the Biologic Price Competition and Innovation Act, suggesting that if biosimilars were not allowed to share the same name it would undermine "the safety and accessibility of affordable biosimilars." The FDA had been in support of allowing biosimilars to share generic names, but the sudden removal of a page from the FDA website that contained a 2006 statement supporting same-name biosimilars prompted the concern of the senators. ■

FDA Actions

The FDA is recommending that hydrocodone-containing pain medications (Vicodin, Norco,

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Lortab, and others) be upgraded from schedule III to schedule II. The move would put significant restrictions on the drugs, including requiring a physician signature for each prescription, no refills, and no phone or fax prescriptions. Hydrocodone would join other powerful opioids including oxycodone, morphine, fentanyl, and methadone in the more restricted schedule II category. The FDA is reacting to the epidemic of prescription drug abuse and addiction that has decimated some communities in this country and has led to the overdose by tens of thousands, including teenagers and young adults. Prescription drug overdoses now outnumber illegal drug overdoses 3:1. The Drug Enforcement Agency has been pushing for stronger controls on hydrocodone for years, but physician and pharmacy organizations have successfully argued that the change unfairly impacts legitimate patients and would increase physician and pharmacy workloads. Hydrocodone/acetaminophen combination drugs were the most frequently prescribed medications in the United States last year. The change is likely to take effect by mid-2014.

Meanwhile, the FDA has approved an extended-release hydrocodone product for the management of severe pain requiring daily, around-the-clock treatment. The drug is an extended-release formulation of hydrocodone that is dosed twice a day. It is available in six strengths — 10, 15, 20, 30, 40, and 50 mg capsules. Because of concerns of addiction and abuse, and the greater risk of overdose and death associated with extended-release and long-acting formulations, hydrocodone extended-release should be reserved for patients in whom alternative treatment options are ineffective, not tolerated, or one otherwise provides inadequate pain management. The approval of hydrocodone extended-release was controversial given that the drug is not packaged as a tamper-proof capsule, theoretically allowing it to be crushed, chewed, or even injected. Experience with abuse of extended-release oxycodone (OxyContin) prompted the FDA to require Purdue Pharmaceuticals to reformulate the drug into a tamper-proof capsule in 2010. Some in the FDA felt this new formulation of hydrocodone should be similarly packaged, but the drug was approved without such restrictions. Hydrocodone extended-release will be schedule II, and marketed by Zogenix Inc. as Zohydro.

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The FDA has approved two new drugs to treat pulmonary arterial hypertension (PAH). Macitentan is a dual endothelin-receptor antagonist, while riociguat is a first in class soluble guanylate cyclase stimulator. Macitentan is a once-daily pill that is approved to treat PAH. Its safety and efficacy was established in a 2-year, randomized, placebo-controlled trial of 742 patients. Patients in the active treatment group had delayed progression of the disease and improved symptoms. Macitentan is manufactured by Actelion Pharmaceuticals and will be marketed as Opsumit. Riociguat is also an oral agent given three times a day. It is approved for PAH and also for chronic thromboembolic pulmonary hypertension (CTEPH), the first drug to be approved for this latter indication. Safety and efficacy for PAH was shown in a trial of 443 patients in which treated patients had improved 6-minute walk times after 12 weeks. It was shown to be effective for CTEPH in a study of 261 patients in which treated patients had improved walk times at 16 weeks. Riociguat is marketed as Adempas by Bayer HealthCare.

An FDA advisory group has recommended approval of simeprevir and sofosbuvir, two long-awaited agents to treat hepatitis C virus (HCV). Both are oral drugs and have higher cure rates compared with currently available agents. Simeprevir is a protease inhibitor, similar to currently available agents such as telaprevir and boceprevir, while sofosbuvir is a new type of hepatitis c antiviral called a nucleotide analogue (or "nuke"). Sofosbuvir has been highly anticipated as clinical trials suggest that it results in sustained virological responses as high as 90%, and may eventually be part of an all-oral regimen for HCV along with ribavirin. The FDA is expected to approve both drugs by mid-December. Simeprevir will be marketed by Johnson & Johnson while sofosbuvir will be marketed by Gilead Sciences. ■