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Clinical Oncology [ALERT]

A monthly update of developments in cancer treatment and research

ABSTRACT & COMMENTARY

Finally, Demonstrable Improvement in Remission Induction for Adult Acute Myelogenous Leukemia

By Jerome W. Yates, MD

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

SYNOPSIS: A multi-institutional study examined the addition of a purine analog, either cladribine or fludarabine, to the standard induction regimen ("7 & 3") in adult patients 60 years of age and younger with acute myelogenous leukemia, and found improved outcomes for those receiving cladribine. The added benefit from cladribine appears to be the result of a reduction in the incidence of resistant disease. The study arm containing cladribine, daunorubicin, and cytarabine yielded an overall survival at 3 years of 45% while conventional "7 & 3" therapy was only 33% at 3 years. Cladribine added to daunorubicin and cytarabine during remission induction improves leukemia control and patient survival for those 60 years of age and younger.

SOURCE: Holowiecki J, et al. Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: A multicenter, randomized phase III study. *J Clin Oncol* 2012;30:2441-2448.

This paper reports a three-arm study randomizing 652 previously untreated acute myelogenous leukemia (AML) patients to one of three arms: 1) conventional "7 & 3" with daunorubicin and cytarabine, 2) the same plus cladribine, or 3) the same plus fludarabine. There were no differences in known prognostic factors, including the distribution of favorable and unfavorable karyotypes, among those randomized. Overall survival at three years was 33% for group 1, 45% for group 2, and 36% for group 3. The addition of cladribine decreased leukemic resistance. Early mortality was similar for all three treatment arms studied. Cladribine can induce direct mitochondrial injury causing cell death, a molecular mechanism of action different from fludarabine. It appears to affect both proliferating and non-proliferating cell pools.

COMMENTARY

Seven days of cytarabine and 3 days of daunorubicin became standard induction therapy for AML in the early 1980s.[1,2] A series of studies exploring modifications, such as doubling the dose of cytarabine, extending its infusion to 10 days, or adding other drugs such as oral thioguanine,

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demonstrated no improvement in the rates of remission.[3] Additional attempts to improve the standard of care included substituting other anthracyclines in place of daunorubicin or increasing its dose; these failed to substantially improve the outcomes. Genetic risk stratification has resulted in improved prediction of outcome results based on good risk and poor risk karyotypes.

Though "7 & 3" has been the "gold standard" AML induction treatment for decades, the data presented offer a cogent rationale to consider adding cladribine. It would appear, based on this credible multi-institutional study, that the addition of cladribine to ara-c and daunorubicin will result in an increase in survival of adults age 60 and younger when treated for acute myelogenous leukemia. ■

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ILLUSTRATIVE CASE SERIES

Adjuvant Management of Uterine Leiomyosarcoma

By William B. Ershler, MD

A 78-year-old female had been generally well with no known chronic medical conditions and was taking no medications when she presented to her primary care physician with lower abdominal pain and urinary frequency of one month's duration. Physical examination at the time revealed a well-appearing woman with normal vital signs and no abnormal physical findings except a palpably enlarged uterus by bimanual pelvic examination. CT scan confirmed the presence of a uterine mass suspicious for malignancy. She was referred to a gynecologic oncologist and had a total abdominal hysterectomy and salpingo-oophorectomy with partial infracolic omentectomy and pelvic debulking of what appeared to be a large (15 cm) tumor mass. Final pathology was high-grade leiomyosarcoma with microscopic invasion of the colon and bladder.

Following an uneventful postoperative course and just prior to hospital discharge, an oncology opinion is requested regarding recommendations for additional management. The gynecologic oncologist noted that although all gross tumor was resected, he remained suspicious of residual microscopic disease.

At the time of consultation, the patient appears better than what might be expected. There is slight pallor, but vital signs were normal, and for the most part, she was free of pain and ambulating without assistance. Cardiac and pulmonary examinations were normal. Laboratory studies revealed her hemoglobin to be 10.4 g/dL and her white blood count was 12,800 per cu mm. Serum electrolytes, creatinine, and liver function tests were all within normal limits. The patient lives with her family and has an excellent network of support within the nearby community.

DISCUSSION

In general, uterine sarcomas are minimally sensitive to chemotherapy and the role for adjuvant systemic treatment has not been established. Nonetheless, leimyosarcomas are particularly aggressive with very high recurrence rates both locally and at distant sites.[1,2] It appears the risk of recurrence at distant sites relates directly with the size of the primary tumor.[3]

In an effort to reduce local recurrence, various radiation approaches have been examined,[4-7] but to date there has been no clearly demonstrated improvement in survival. In fact, in an EORTC trial, adjuvant RT was disappointing in that

treatment resulted in neither improved survival nor local control.[8] Thus, it remains unclear whether adjuvant radiation is of value for patients with leiomyosarcoma; typically, it is reserved for patients with high likelihood of local recurrence, such as those with large primary tumors.

There is, however, stronger rationale for adjuvant systemic therapy based on the high rate of recurrence at distant sites. A number of observational studies suggest that single agents or combinations thereof afford some improvement in overall survival,[9,10] whereas others have suggested no benefit.[11] In one prospective trial of gemcitabine and docetaxel administered to 25 patients with high-grade uterine leiomyosarcoma (stages I-IV), there was a 2-year progression-free survival rate of 40%,[12] a rate comparing favorably to historic controls and providing rationale for further investigation of this combination or others in the adjuvant setting.

RECOMMENDATIONS

Although the current patient is 78 years old, she previously had been healthy and remained physiologically intact throughout recent major surgery. The tumor resected was large, high-grade, and with demonstrable invasion into surrounding tissue including colon and bladder. It would appear the chance of local and or distant recurrence would be close to 100%. With this in mind, my recommendation would be to undertake a course of adjuvant radiation followed by systemic chemotherapy. Depending on performance status after radiation, I would either recommend gemcitabine alone or in combination with docetaxel. In light of the lack of strong evidence for this approach, it also would be perfectly reasonable to suggest supportive care alone, acknowledging the very high likelihood of recurrence with or without treatment and thereby avoiding the possible treatment associated toxicity. As always, I would look to the patient and family for guidance, formulating a final treatment plan based upon informed goals and expectations. ■

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ABSTRACT & COMMENTARY

Adjuvant Chemotherapy for Older Patients with Colon Cancer

By Gary R. Shapiro, MD

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

SYNOPSIS: **Four large data sets were analyzed to evaluate the effect of adjuvant treatment on survival in patients with stage III colon cancer diagnosed after age 75. While adjuvant chemotherapy was associated with a survival benefit, oxaliplatin-based regimens offered no more than a small incremental benefit over non-oxaliplatin-containing regimens.**

SOURCE: Sanoff HK, et al. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol* 2012;30:2624-2634.

To assess outcomes in the general population of older patients, Sanoff and her colleagues gathered data from four observational data sources: the Surveillance, Epidemiology, and End Results registry linked to Medicare claims (SEER-Medicare); the New York State Cancer Registry (NYSCR) linked to Medicare claims; the Cancer Care Outcomes Research & Surveillance Consortium (CanCORS); and the National Comprehensive Cancer Network (NCCN) Outcomes Database. All 5489 patients had stage III adenocarcinoma of the colon (excluding rectal cancer), received chemotherapy within 120 days of surgery, and were 75 years or older at the time of diagnosis.

Use of adjuvant chemotherapy declined with age and comorbidity. Multivariate analysis showed age to be the most strongly associated factor: 63% of patients aged 75 to 79 years, 43% of those aged 80 to 84 years, and 14% of patients 85 years of age and older. The same SEER-Medicare analysis found 46% of patients in the 75 to 79 age group who were treated with chemotherapy received oxaliplatin, compared to 25% of the 80 to 84 group and only 7% of those aged 85 years and older.

Survival was better in those patients who received adjuvant chemotherapy than those who did not (HR 0.60; 95% confidence interval [CI], 0.53 to 0.68 in the SEER-Medicare analysis), but the incremental benefit of oxaliplatin over non-oxaliplatin-containing regimes was seen in only two of the three data sets analyzed (SEER-Medicare HR 0.84; 95% CI, 0.69 to 1.04; NYSCR-Medicare HR 0.82, 95% CI, 0.51 to 1.33).

COMMENTARY

Half of colorectal cancer deaths occur in people older than age 75, and 40% of all colorectal cancer diagnoses are in those 75 years of age or older. Sanoff's database analysis of the 40% in this group who present with stage III disease showed that many do not receive life-saving adjuvant chemotherapy,[1] despite overwhelming data in this and others studies[2,3,4] that the benefits of adjuvant chemotherapy in older patients are similar in younger and older individuals.

Of note is Sanoff's observation that elderly black patients appear less likely to receive adjuvant chemotherapy than their white counterparts. Although the small sample size included too few African Americans to draw any definite conclusions, this would not be inconsistent with other reports,[5] and it should remind us of the urgent need to develop strategies to overcome health care disparities in minority and underserved populations. Sanoff found that those patients 75 years of age and older treated with adjuvant chemotherapy had a markedly lower risk of death than those who did not receive treatment (32% vs 47% 3-year death rate in the SEER-Medicare database). This effect was comparable to that in previously published studies. This is particularly significant given the fact that more than three-quarters of stage III colon cancer recurrences are within 3 years of diagnosis, well under the life expectancy of the average 75-year-old (9 to 12 years) or 85-year-old (5 to 7 years). Even an unhealthy 75-year-old man or woman will live 5 to 7 more years; long enough to suffer symptoms and early death from recurrent colon cancer.

Although previous subgroup analyses of key randomized, controlled trials showed equal efficacy in seniors getting adjuvant chemotherapy for stage III colon cancer, Sanoff et al wanted to see if this benefit was just as prevalent in older patients treated outside of a formal clinical trial in the community setting. Indeed, they found that the survival value of adjuvant chemotherapy was remarkably similar.

Sanoff and her colleagues believed that this type of comparison was especially warranted when considering the role of oxaliplatin in adjuvant colon cancer regimens. Although oxaliplatin increased cure rates in clinical trials, these studies included very few patients 75 years or older.[4] Both the SEER-Medicare and NYSCR-Medicare database analyses confirmed the previously reported 5% absolute improvement in survival at 3 years in patients treated with oxaliplatin-based regimens, but, like the formal clinical trials, the relatively small sample sizes in the database analyses limited Sanoff's ability to draw definitive conclusions about the benefit of these regimens in the elderly.

Unfortunately, this study does not shed much light on the quality-of-life considerations that often are more important than longevity when deciding whether to treat older individuals with cancer. This is especially important when one considers the relatively high incidence of oxaliplatin-induced peripheral neuropathy that can lead to debilitating mobility abnormalities and falls in older individuals. Diarrhea, mucositis, nausea, and vomiting also are more frequent with oxaliplatin-containing regimens. Even though older patients appear to be at no more risk of these side effects than younger patients,[2] they are susceptible to adverse events related to secondary dehydration.

Like the randomized, controlled studies, the Sanoff analysis establishes the efficacy and safety of adjuvant chemotherapy in elderly colon cancer

patients. It also calls attention to the holes in our knowledge due to the lack of sophisticated geriatric assessments that help determine risk and benefit in this heterogeneous group of patients. ■

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ABSTRACT & COMMENTARY

Pemetrexed in the Treatment of Relapsed/Refractory Primary Central Nervous System Lymphoma

By Mamatha Prabhakar, MD

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

SYNOPSIS: In this Phase 2 trial, 11 patients with relapsed/refractory primary central nervous system lymphoma after high-dose, methotrexate-based regimen were treated with pemetrexed 900 mg/m^2 every 3 weeks, dexamethasone 4 mg bid, folate, and B12 supplementation. The treatment had an overall response rate of 55%, disease control rate of 91%, median progression free survival of 5.7 months, and median overall survival of 10.1 months. Toxicities were more than expected with the standard pemetrexed dose (500 mg/m^2) and were primarily hematologic and infectious, which were easily managed. Although single-agent activity of pemetrexed in this study is novel and promising, optimal dosing and efficacy need to be studied further.

SOURCE: Raizer JJ, et al. Pemetrexed in relapsed/refractory PCNSL. *Cancer* 2012;118:3743-3748.

Nearly one-half of primary central nervous system lymphomas (PCNSL) occur in patients older than 60 years and about 90% are diffuse large B cell lymphomas. Although R-CHOP is effective for systemic lymphoma, similar approaches for PCNSL have failed to produce durable disease control. Untreated patients survive only a few months. Although whole-brain radiation therapy improves survival, it is associated with significant neurologic toxicity and its use is limited. High-dose, methotrexate-based regimens have demonstrated superior overall survival of 30-50 months.[1] However, despite this, PCNSL almost uniformly results in recurrence or progression and death. Expectant survival after relapse is about 4-8 months.[2] No standard salvage treatment for relapsed or refractory disease exists. Although numerous approaches including radiation, chemotherapy (temozolamide, etoposide), and/or rituximab have been attempted, these have resulted in variable degrees of demonstrable activity. With the poor outcomes linked to PCNSL, there is a constant quest to identify a novel agent that is effective, safe, and easy to administer. Pemetrexed is a rational strategy for therapeutic palliation of recurrent or progressive PCNSL. Its mechanism of action is similar to methotrexate but it has the advantage of targeting more than one site of folate synthesis, convenient administration, single-agent efficacy, established management algorithms, outpatient administration, and its evidence of safety and efficacy in systemic malignancies. The authors conducted this trial using pemetrexed in patients with relapsed/refractory PCNSL to determine single-agent activity. Enrolled subjects had a Karnofsky performance of > 60. Based on preclinical data suggesting limited penetration into the central nervous system, a dose higher than standard (900 mg/m^2 rather than 500 mg/m^2) was chosen.[3] Eleven patients were treated on 6-week cycles with pemetrexed 900 mg/m^2 administered on days 1 and 21. Patients received dexamethasone 4 mg bid on the day before, the day of, and the day after each infusion of pemetrexed, and all patients were supplemented with folic acid and B12. Patients remained on the treatment until disease progression or intolerable side effects occurred. Those attaining CR received two additional doses. MRI was done every 6 weeks.

The authors observed a CR rate of 36%, PR rate of 19%, overall response rate (CR+PR) of 55%, and a disease control rate (CR+PR+SD) of 91%, all of which match favorably with other tested novel agents (e.g., temozolomide single-agent: relative risk [RR] 31%, progression-free survival [PFS] 2.8 months, and overall survivial [OS] 3.9 months).[4] The PFS at 6 months and 12 months were 45%

(95% confidence interval [CI], 16%-74%) and 27% (95% CI, 20%-70%), respectively, with a median PFS of 5.7 months (95% CI, 1.6-21.4 months). The median OS was 10.1 months (95% CI, 2.4-33.3 months). Most common toxicities were hematologic (cytopenias), including one patient with neutropenic pneumonia. One patient had dose reduction for hematologic toxicity and one patient discontinued due to grade 3 thrombocytopenia. The authors believe the toxicities seen in this study were related to using higher than standard dose (900 mg/m^2).

COMMENTARY

Despite the aggressive upfront use of high-dose, methotrexate-based chemotherapy, PCNSL almost uniformly results in recurrence, progression, and death. Its rare presentation, incomplete molecular and biological understanding, and difficulty in execution of prospective trials has limited the identification of new therapeutic agents. Despite these unfavorable features, there has been progress, and different agents have been tried with comparable activity including temozolomide, etoposide, rituximab, and now pemetrexed. Although combination salvage regimens like PCV (procarbazine, CCNU, vincristine) have shown higher response rates (86%) and OS of 16 months, these have proven difficult to administer because of associated increased toxicity. It is interesting to note that pemetrexed showed single-agent activity in patients who had failed earlier high-dose methotrexate therapy. All patients also received dexamethasone during pemetrexed treatment and this might have contributed to the response rates. Preclinical studies have shown limited CNS penetrance for pemetrexed, although slightly better than methotrexate. Its easy outpatient administration is an advantage over other agents that require hospitalization. With the use of higher doses of pemetrexed (900 mg/m^2) to improve CNS penetration, toxicities seen were more than expected. In future clinical trials using high-dose pemetrexed, it will be interesting to see if leucovorin instead of folic acid will be able to minimize the toxicities. If pemetrexed is chosen for treatment, pneumocystis prophylaxis should be considered, as two of 11 patients developed PCP pneumonia. Clinical trials testing higher doses of pemetrexed are underway and might add more information on the pharmacokinetics, improved CNS penetration, and safety. ■

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ABSTRACT & COMMENTARY

Dietary Lignan Intake and Breast Cancer Risk

By Donald J. Brown, ND

Director, Natural Product Research Consultants, Seattle, WA

Dr. Brown is a consultant to the supplement industry. He reports no financial relationships relevant to this field of study.
This article originally appeared in the August 2012 issue of *Integrative Medicine Alert*.

SYNOPSIS: **In this case-control study, dietary lignan intake was inversely associated with risk of breast cancer in both premenopausal and postmenopausal women. Also noted were more favorable prognostic characteristics associated with lignan intake, especially in premenopausal women.**

SOURCE: McCann SE, et al. Dietary intakes of total and specific lignans are associated with clinical breast tumor characteristics. *J Nutr* 2012;142:91-98.

To evaluate the relationship between dietary lignan intake and breast cancer as well as tumor characteristics, the researchers investigated dietary intakes of total and specific lignans in 683 women with breast cancer and 611 healthy women enrolled in the Data Bank and BioRespository (DBBR) at Roswell Park Cancer Institute (RPCI) in Buffalo, NY. The total population of premenopausal women was 214 with breast cancer (mean age 44.6 years) and 202 controls (mean age 44.4 years). In the group of postmenopausal women, there were 469 with breast cancer (mean age 63.7 years) and 409 controls (mean age 62.1 years). Clinicopathologic data were obtained from the RPCI breast cancer database. The data were linked with epidemiologic data from the DBBR and included tumor stage and grade, estrogen receptor (ER) and progesterone

receptor (PR) status, and HER2 protein expression. Daily intakes of total lignans and found individual lignans (matairesinol, lariciresinol, pinoresinol, and secoisolariciresinol) were obtained from a food frequency questionnaire that was part of the DBBR. Odds ratio [OR] and 95% confidence interval [CI] for associations between daily intakes of total and specific lignans with clinicopathologic characteristics compared to women without breast cancer were estimated.

Women in the highest compared to the lowest tertile of total lignan intakes had approximately 40-50% lower odds of having breast cancer. Higher total lignan intakes also were associated with significantly reduced odds of having an invasive tumor, especially among premenopausal women (OR 0.48 [95% CI 0.26-0.86] for premenopausal women and OR 0.70 [95% CI 0.47-1.06] for postmenopausal women).

The reductions in risk of breast cancer and invasive cancer were linked primarily to higher intakes of lariciresinol and pinoresinol in premenopausal women and of lariciresinol and matairesinol in postmenopausal women. For premenopausal women, there was a borderline significant 50% reduction in odds of having either stage I or II breast cancer but no association with higher stages. The association was strongest for the lignans lariciresinol and pinoresinol. In postmenopausal women, there was a significant 50% reduction only in stage I cancers that was associated with increased intake of matairesinol. Higher total lignan and matairesinol intakes were associated with lower risk of grade 3 tumors, primarily among premenopausal women.

Higher total lignan intakes were strongly inversely correlated with risk of ER^- breast cancer among premenopausal women (OR 0.16 [95% CI 0.03-0.44]) independent of the specific lignan. Among postmenopausal women there was an inverse correlation related to ER^+ breast cancer that was predominantly associated with lariciresinol and matairesinol intakes. Higher intakes of total lignans were associated with both negative and positive HER2 status in premenopausal women, with the estimates much stronger for $HER2^+$ (OR 0.21 [95% CI 0.05-0.87]) than $HER2^-$ (OR 0.56 [95% CI 0.30-1.05]). There was no association between total lignan intakes and HER2 status in postmenopausal women, but there was a lower risk of $HER2^+$ tumors in those consuming higher amounts of matairesinol (OR 0.36 [95% CI 0.14-0.89]). Among premenopausal women, those in the highest tertile of total lignan intake had greatly reduced odds of having triple negative tumors compared to those in the lowest tertile (ER^-, PR^-, $HER2^-$; OR 0.16 [95% CI 0.04-0.62]). This reduction was primarily associated with lariciresinol and pinoresinol.

COMMENTARY

The results of this ambitious study expand on previous epidemiological studies that have found an inverse correlation between dietary lignan intake and breast cancer risk (please note brief review below) by adding more detailed data on reduced risk of specific types of cancer as well as prognosis. Lignans are naturally occurring diphenolic compounds that are classified as phytoestrogens.[1] Commonly found in whole grains, seeds, nuts, legumes, fruit, and vegetables, the highest concentrations are currently found in flaxseed powder extracts standardized to secoisolariciresinal and a 7-hydroxymatairesinol (HMR) powder extracted from the knot wood of Norwegian Spruce.[1,2] The researchers report in the Discussion section of the paper that the primary sources of total lignans in the study population were apricots, broccoli, berries, coffee, and red wine. The primary sources of matairesinol intakes were onions, oranges, "salty snacks," peaches, and coffee. The primary sources of lariciresinol were broccoli, winter squash, berries, apricots, and coffee. Interestingly, they did not include flaxseed or tea in the list of foods or beverages.

Dietary lignans are converted by gut microflora to the mammalian lignans enterolactone (ENL) and enterodiol (END). Matairesinol and HMR are directly converted to ENL while pinoresinol, lariciresinol, and secoisolariciresinal are first converted END, which then partially converts to ENL.[1] One study found that sesame seeds, a rich source of matairesinol, more efficiently raised ENL levels when compared to flaxseed.[3]

Several, but not all, epidemiological studies have reported reduced risks of breast cancer associated with either increased intake of dietary lignans and/or higher blood levels of ENL.[4] A case-control study of premenopausal women found that overall breast cancer risk was inversely correlated with plasma ENL.[5] Another found an inverse correlation between breast cancer risk and plasma ENL in both premenopausal and postmenopausal women.[6] Two additional studies found that increased plasma ENL was associated with a significant decrease in risk of ER^- breast cancer in premenopausal[7] and postmenopausal women.[8] Finally, in a large case-control study, higher dietary lignan intake and serum levels of ENL and END were associated with a significantly reduced risk of ER^- and PR^+ breast cancer in postmenopausal women.[9]

As pointed out by the authors of this new study, ER^- tumors are more common among younger

women and have a poorer prognosis because of fewer treatment options.[10] While less common, triple negative breast cancer also has a poor prognosis due to lack of effective treatments. The identification of simple modifiable lifestyle changes such as increased lignan intake could potentially reduce the occurrence of less favorable tumor types, and perhaps have a considerable impact toward reducing the burden of the disease in both premenopausal and postmenopausal women. ■

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CME Instructions

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

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.

CME Questions

1. The addition of which drug to the standard "7 & 3" regimen recently was demonstrated to improve remission induction for patients with acute myelogenous leukemia?

a. Fludarabine
b. Ifosfamide
c. Cladribine
d. Etoposide

2. For patients with high-grade leiomyosarcoma, which of the following statements is true?

a. Adjuvant radiation therapy has been demonstrated to reduce local recurrence rates and improve overall survival.
b. Adjuvant systemic chemotherapy has been demonstrated to reduce distant recurrence rates and improved overall survival.
c. Neither a nor b.
d. Both a and b.

3. The dose of pemetrexed used in the clinical trial to treat relapsed/refractory primary central nervous system lymphomas was:

a. 500 mg/m^2 administered every 3 weeks
b. 500 mg/m^2 administered every 2 weeks
c. 900 mg/m^2 administered every 2 weeks
d. 900 mg/m^2 administered every 3 weeks

[IN FUTURE ISSUES]

Sunitinib for advanced breast cancer

Clinical Briefs in Primary Care™

The essential monthly primary care update

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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Risk for Zoster from the Vaccine in Immunosuppressed Persons

Source: Zhang J, et al. *JAMA* 2012;308: 43-49.

The prevailing wisdom suggests that because herpes zoster vaccine (ZOS) is a live virus, it should not be administered to persons receiving immunosuppressive treatments, such as biologic agents or methotrexate for rheumatoid arthritis, or chronic prednisone therapy of 20 mg/d or more. The concern is that instead of mounting an immune response to the vaccine, vaccinees might actually experience a case of shingles as a result of the vaccine.

To examine the real-life risk of an acute zoster infection after ZOS, a retrospective analysis was performed on a large Medicare database (n = 463,541) of persons with a diagnosis of rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease. Any one of these disorders would be commonly treated with immunosuppressive agents, corticosteroids, or both.

The analysis looked at the number of cases of shingles within 42 days of ZOS, anticipating that if the live virus vaccine had induced shingles, it should certainly have happened within that 6-week window after vaccination.

No increased incidence of shingles was seen in ZOS recipients, even in patients on biologics. Indeed, ZOS was associated with a 39% lower risk of shingles during the 42-day window of observation, and a reduced risk during the subsequent 2 years (median) of follow-up. ZOS appears to be beneficial even in immunocompromised individuals, and the authors challenge the propriety of current recommendations that advise against ZOS administration in such populations. ■

Cerebral Aneurysms: What's in Your Patient's Future?

Source: UCAS Japan Investigators. *N Engl J Med* 2012;366:2474-2482.

The UCAS (unruptured cerebral aneurysm) Japan study began enrolling patients with incidentally discovered cerebral aneurysms (CRAs) for an observational study in 2001. The primary purpose of the study was to better delineate the natural history of incidentally discovered CRAs (as opposed to discovery through neurologic signs or symptoms). Prior to this trial, it had been generally recognized that CRAs < 7 mm rarely rupture, and that posterior circulation CRAs have a greater risk than anterior.

This prospective cohort study included patients (n = 6413) with incidentally discovered CRA and minimal, if any, disability. Subjects were followed for up to 8 years. During this interval, the annual rate of CRA rupture was approximately 1%. When rupture did occur, it was fatal in 35% of cases, or led to moderate-severe disability in another 29%.

The most important predictive factors for rupture were size of the CRA, age, and gender (females are at greater risk). For example, when compared with lesions < 7 mm, a 7-9 mm lesion had a three-fold increase of rupture, and a lesion > 10 mm had a nine-fold increased risk. Risk in women was 1½ times as great as men, and persons over age 70 were 21% more likely to experience aneurysm rupture. Because the entire population of enrollees was Japanese, the generalizability of these results may have limitations, but nonetheless provide perhaps the most accurate mapping of risk factors for rupture of CRAs. ■

Elucidating the 'Best' Interval for Bone Density Screening in Osteoporosis

Source: Yu EW, Finkelstein JS. *JAMA* 2012;307:2591-2592.

Once a baseline bone mineral density (BMD) has been obtained, it is unclear when the study should be repeated. For one thing, the literature suggests that only about 30% of bone strength may be attributable to bone density. Additionally, some of the interventional trials using bisphosphonates have found fracture reduction despite continuation of bone density *loss* over the first year or two of intervention. Finally, the rate at which BMD declines has been linked to the baseline BMD.

For instance, a study that looked at menopausal women (age > 67 years) for progression of BMD loss found some fairly startling results: It would take approximately 15 years for 10% of women with normal baseline BMD (T score < -1.5) to incur sufficient loss of BMD to cross the diagnostic threshold for osteoporosis (T score < -2.5). Similarly, for women with osteopenia (T score -1.5 to -2.0) at baseline, it would require 5 years for 10% of

them to progress to frank osteoporosis. At the greatest level of osteopenia (T score -2.0 to -2.5), progression to osteoporosis in 10% of women would be expected to occur within 1 year. These projections assume no addition of new risk factors known to accelerate bone loss.

Although it is tempting to get BMD more often, it may not be helpful. Although the data are sufficiently uncertain that the USPSTF has been unable to provide confirmation of a preferred schedule, Yu et al suggest following rescreening intervals for postmenopausal women: for women with normal BMD at baseline, 10 years; for women with mild osteopenia and low FRAX score at baseline, 5-10 years; for women with moderate osteopenia or FRAX score approaching treatment threshold, 2 years. ■

An Unexpected Connection Between PTSD, ACE Inhibitors, and ARBs

Source: Khoury NM, et al. *J Clin Psychiatry* 2012;73:849-855.

Several lines of evidence suggest that modulation of the renin-angiotensin-aldosterone system with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) might potentially have positive effects on post-traumatic stress disorder (PTSD). Preclinical data indicate favorable cerebral effects of ARBs, such as stress reduction and anxiolysis. Some ARB trials have reported positive effects on cognition, quality of life, and depression or anxiety.

Khoury et al performed a cross-sectional observational data analysis of PTSD patients (n = 505) comparing symptoms in those who were being treated with an ARB/ACE vs controls (no ARB/ACE treatment). Overall, PTSD symptom scores were almost 25% lower among patients treated with ACE or ARB therapy ($P = 0.04$).

The better symptom scores among PTSD patients treated with ARB or ACE therapy were not simply due to the fact that hypertension (which is more common in PTSD patients) was treated; no other antihypertensive medications (e.g., calcium channel blockers, diuretics, beta-blockers) were found to have similar favorable effects.

The mechanism through which ACE/ARB treatments impact PTSD is not well established, but may be through modulation of the noradrenergic system. ■

The Right Amount of Vitamin D to Prevent Fractures

Source: Bischoff-Ferrari HA, et al. *N Engl J Med* 2012;367:40-49.

Inclusion of vitamin D (VTD) in the regimen for fracture prevention is time honored and condoned by major guidelines. Intuitively, VTD should be helpful, but the analyses of data in reference to this topic are mixed. For instance, although one meta-analysis indicated an 18% reduction in hip fracture if a minimum of 482 IU/d VTD was prescribed, equally prominent data concluded that VTD alone was of *no benefit*. So, how about further investigation of the subject?

Bischoff-Ferrari et al performed an analysis on 11 double-blind, randomized, controlled trials of oral VTD supplementation (n = 31,022) seeking to determine if supplementation (with or without calcium) reduced hip fracture. According to their analysis, there was no statistically significant reduction in fracture risk in subjects assigned to VTD. Story over? Well, maybe not quite.

First, although hip fracture was not reduced, there was a marginally statistically significant 7% reduction of total non-vertebral fractures. Additionally, when analyzed from the viewpoint of the *actual intake* of VTD instead of what subjects were assigned to, the picture looks quite different. Specifically, subjects in the highest quartile of actual VTD intake (prescribed supplementation plus dietary intake) enjoyed a statistically significant 30% reduction in hip fracture. For the time being, at least 800 IU/d VTD supplementation is recommended in persons ≥ age 65. ■

Prevention of Diabetes

Source: Perreault L, et al. *Lancet* 2012; 379:2243-2251.

It appears that one's ounce of prevention may have to be weighed more carefully to attain the fullest pound of cure. Why? The answer lies in subgroup analysis of recent trials in diabetes prevention.

There have been many diabetes prevention trials, essentially all of which have been successful to a varying degree. Overall, diet and exercise appear to be as efficacious as any other intervention. Pharmacologically, numerous classes of agents have been successfully tried (metformin, thiazolidinedione, alpha-glucosidase inhibitor, etc.). What has been learned is that successful incorporation of diet/exercise or pharmacotherapy over a 4- to 6-year period reduces the likelihood of progressing from prediabetes to diabetes (typically, 6-10%/year) by half or more. But there is more to the story.

After successful treatment (pharmacotherapy or lifestyle), the majority of those who are prevented from progressing to frank diabetes still fulfill criteria for prediabetes (A1c 5.7-6.4). Between 20-50% of treated subjects are restored to currently recognized normal glucose levels.

The analysis by Perrault et al indicates that persons with prediabetes in whom normal glucose homeostasis was restored are half as likely to progress to frank diabetes over a 3-year, post-trial observation period as individuals whose glucose control was improved, but still reflected prediabetes. Striving for the best glucose control in prediabetes may have long-term benefits. ■

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Does Finasteride Cause Permanent Sexual Side Effects?

In this issue: Side effects of finasteride; new ruling on pharmaceutical companies paying generic manufacturers; and FDA actions.

Sexual side effects of finasteride

Finasteride — the popular drug used to treat male pattern baldness and symptomatic benign prostatic hypertrophy — may cause long-term sexual dysfunction, according to a new study. Several recent studies have shown that the drug, which is marketed as 1 mg (Propecia) and 5 mg (Proscar), can cause sexual side effects that persist after stopping the drug in as many as 20% of men. In April, the FDA required new labeling for both strengths regarding libido, ejaculation, orgasm disorders, and even infertility that may persist after treatment ends. The new study looked at 54 men, with an average age of 31, who reported ≥ 3 months of sexual side effects after taking the 1 mg strength for male pattern baldness. All men were previously healthy without previous history of sexual dysfunction, medical conditions, psychiatric conditions, or prescription medication use. After 9-16 months of follow-up, 96% of subjects reported persistent sexual side effects (based on the Arizona Sexual Experience Scale). The duration of finasteride use did not correlate with changes in sexual dysfunction scores. The authors urge prescribers of finasteride to warn men of potential adverse effects (*J Sex Med* published online July 12, 2012). ■

Pharmaceutical company ruling

Is it legal for pharmaceutical companies to pay generic manufacturers to keep their products off the market? Until now it has been. Brand-name manufacturers have written enormous checks to keep their low-cost generic competitors off the market. That may change, however, after a federal appeals court in Philadelphia ruled that the practice is anticompetitive, a decision that is counter to three previous federal circuit courts rulings. *The New York Times* cites the example of Bayer Pharmaceuticals which paid generic drug maker Barr Laboratories and other generic houses $400 million to withhold their generic version of ciprofloxacin, their $1 billion a year blockbuster antibiotic. The case could eventually end up at the Supreme Court. At stake is billions of dollars in lost profits for pharmaceutical manufacturers, but an equal amount of savings for Medicare/Medicaid, health plans, and consumers. ■

FDA actions

The FDA has approved the second new weight-loss medication within a month. The new product combines phentermine along with topiramate in an extended-release product. Phentermine has been marketed since 1959 and was part of the infamous "fen-phen" combination that was popular in the 1990s (fenfluramine was eventually banned due to cardiac valvulopathy in 1997). Topiramate is currently marketed as an anticonvulsant and for migraine prophylaxis as Topamax. The combination was rejected by the

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FDA in 2010 due to safety concerns, but Vivus Pharmaceuticals submitted additional data to the agency and recently won approval in July. In the process, the company changed the brand name from Qnexa to Qsymia. Similar to the recently approved lorcaserin (Belviq), phentermine/topiramate is approved as an addition to a reduced-calorie diet and exercise for weight management in adults with a BMI of 30 or greater, or with a BMI of 27 or greater with at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. In two placebo-controlled trials, 3700 obese and overweight patients lost an average of 6.7-8.9% of their body weight, depending on the recommended or higher dose therapy (slightly better results than those seen with lorcaserin). Patients who have not lost at least 3% of their body weight by week 12 should discontinue the drug. Because of continued safety concerns, the drug was approved with a Risk Evaluation and Mitigation Strategy (REMS), which consists of a medication guide, prescriber training, and pharmacy certification. The drug cannot be used during pregnancy or in patients with recent stroke or heart disease, and patients should have their heart rates monitored during therapy. Vivus will market Qsymia immediately, but will be required to conduct 10 postmarketing studies to assess safety.

The FDA has approved aclidinium bromide, a dry powder inhaler for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). Aclidinium is a long-acting antimuscarinic agent that works primarily on the M3 receptor causing sustained bronchodilation. The approval was based on three studies of nearly 1300 patients with COPD. The drug may cause anticholinergic side effects, including worsening narrowing-angle glaucoma and urinary retention. It should not be used as a rescue inhaler and is not recommended for those 18 years of age or younger. It is dosed twice a day. Aclidinium inhaler is the second anticholinergic inhaler to be approved after tiotropium (Spiriva), which was approved in 2004. Aclidinium will be distributed by Forest Laboratories and will be marketed as Tudorza Pressair.

The FDA has approved mirabegron to treat adults with overactive bladder. The drug is a novel, once-daily beta-3 adrenergic agonist that works by enhancing storage function and relaxing the urinary bladder, a unique effect and distinct from currently marketed antimuscarinics that inhibit bladder contraction. The once-a-day medication will be available in 25 mg pills. The dose can be increased to 50 mg after 2 months if needed. The approval was based on three placebo-controlled trials that showed statistically significant improvement in incontinence episodes and number of urinations per 24 hours. The most common adverse effects were hypertension, nasopharyngitis, urinary tract infection, and headache. Mirabegron will be marketed by Astellas Pharma as Myrbetriq.

The FDA has approved a new colon cleansing agent for colonoscopy prep. The new prep is sodium picosulfate, magnesium oxide, and citric acid in powder form that is dissolved in water and taken in two doses the night before and the morning of the procedure. It may also be taken the afternoon and the evening before the procedure (Day-Before regimen). The safety and efficacy of the new agent was studied in two studies of about 1200 patients undergoing colonoscopy in which standard PEG plus electrolytes was used as a comparator, and the new prep was found to be at least as effective as the standard prep. Ferring Pharmaceuticals will market the new two-dose prep as Prepopik.

The FDA has approved icosapent ethyl, a new fish oil preparation for the treatment of hypertriglyceridemia. It is approved as an adjunct to diet to treat patients with triglyceride levels greater than 500 mg/dL. The drug contains ultra purified ethyl EPA, an omega-3 fatty acid. The new product follows GlaxoSmithKline's Lovaza, another fish oil that is currently marketed for the same indication and generates more than $1 billion in annual sales. The new product is manufactured by Amarin Corporation and will be marketed as Vascepa. Fish oils are effective at lowering triglycerides but evidence is lacking that they are effective for secondary prevention of cardiovascular disease (*Arch Intern Med* 2012;172:686-694).

An FDA advisory committee has recommended an new indication for Genentech's ranibizumab (Lucentis) for the treatment of diabetic macular edema, an indication for which there is currently no approved therapy. The drug is approved to treat neovascular age-related macular degeneration and macular edema following retinal vein occlusion. Diabetic macular edema is commonly treated with laser therapy, a procedure that has the potential side effect of some vision loss. The FDA generally follows its advisory committee's recommendations and should make a final recommendation later this year. ■