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A monthly update of developments in cancer treatment and research

ABSTRACT & COMMENTARY

Phase 1 Trial of Intraventricular Rituximab and Methotrexate in Heavily Pretreated Patients with Recurrent CNS Lymphoma

By Bindu Kanapuru, MD

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

SYNOPSIS: This Phase 1 clinical trial evaluated the safety and pharmacokinetics of intraventricular immune-chemotherapy with twice weekly rituximab (10 mg and 25 mg) and methotrexate in 14 patients with recurrent central nervous system lymphoma (primary or secondary). Three patients were treated at the 10 mg dose level and 11 patients received treatment with 25 mg of rituximab. No dose-limiting toxicity was seen with this combination at the 10 mg or 25 mg dose level. Coadministration with methotrexate was associated with slower elimination of rituxan from cerebrospinal fluid. The complete response in the leptomeningeal compartment in this heavily pretreated population was 75%, and the overall complete response rate was 43%.

SOURCE: Rubenstein JL, et al. Multicenter phase 1 trial of intraventricular immunochemotherapy in recurrent CNS lymphoma. *Blood* 2013;121:745-751.

Primary central nervous system (CNS) lymphoma is a rare but aggressive lymphoma, accounting for 4-6% of extranodal lymphomas. High-dose methotrexate (MTX) and cytosine arabinoside (Ara-c) is the standard of care for initial treatment of this aggressive lymphoma. However, failure rates are more than 50% and relapse is associated with a very poor prognosis. CNS relapse in patients with primary systemic lymphoma is also associated with a very poor outcome. Although prophylactic intrathecal (IT) therapy is administered to patients identified to be at high risk for CNS relapse, a clear benefit (except in Burkitt's and acute lymphoblastic leukemia) has yet to be established.[1] Addition of rituxan to standard CHOP chemotherapy has been associated with improved survival in systemic non-Hodgkin's lymphoma, but its benefit on decreasing CNS relapse or in the treatment of primary CNS lymphoma is less clear.

The reason for this discrepancy between systemic

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and CNS responses was thought to be due to the poor CNS penetration of the rituxan, and cerebrospinal fluid (CSF) levels of rituxan after intravenous administration were only 0.1% of the serum concentrations. In non-human primates, intrathecal administration of rituxan was shown to produce therapeutic levels in CSF and was well tolerated. In a prior Phase 1 trial with single-agent, intraventricular rituximab, the authors established that intraventricular injection at 10-50 mg reproducibly results in concentrations within the ventricles that are similar to peak levels in the serum achieved after standard intravenous injection of rituximab.[2]

In the current study, the authors conducted a multicenter, Phase 1 trial with intraventicular rituximab and methotrexate, with the rationale that rituximab may enhance the apoptotic effect of chemotherapeutic agents by sensitizing autoimmune B cells.[3]

This trial included 14 heavily pretreated patients (median of five prior regimens) with relapsed or refractory CD20+ CNS lymphoma arising from systemic NHL (8) or primary CNS lymphoma (6) without prior exposure to intrathecal rituximab. Eligible patients were older than age 17 years with Karnofsky performance status more than 50%, were HIV-seronegative, with granulocyte concentration of at least 1000/mcL, and platelet concentration of at least 50 000/mcL and had an Omaya reservoir. Patients had baseline laboratory evaluation as well as staging with slit lamp, MRI, and spinal fluid analysis. Participants were enrolled at two doses: three patients were treated with 10 mg of rituximab alone for the first dose and with 12 mg of methotrexate 3 days later (D4). The treatment was repeated every week with planned treatment for 4 weeks.

CSF studies including cytology were evaluated during the second injection every week. Serum laboratory studies were repeated at the time of the second injection every week. Lymphoma restaging and neuroimaging were done at week 5 and intraocular examination was performed if positive at baseline. PK analysis was done by matched CSF and venous blood samples.

No dose-limiting toxicity (infusional hypertension) was seen at the 10 mg or 25 mg dose levels. Adverse events were self limited and included grade I paraesthesias, chills, and rigors. No events of arachnoiditis were seen. Addition of methotrexate delayed the egress of rituxan from CSF, and the elimination rates (first-order) were 0.88/h and 0.84/h for the 10 mg and 25 mg dose levels, respectively, when rituximab was given alone and 0.47/h and 0.36/h, respectively, when administered in combination with MTX. Two patients were unable to complete treatment (4 weeks) due to disease progression. The overall complete response (CR) was 75% in 12 patients with leptomeningeal involvement at a median of three doses. However, four patients who had CR in the leptomeninges had evidence of parenchymal progression and the overall response rate was only 43% (6/14).

COMMENTARY

The prognosis for relapsed CNS lymphoma is dismal, with median survival of 6 months.[4] No standard therapies exist and the current therapies are often associated with toxicity. This is the first trial to explore the safety of intraventricular immune chemotherapy in patients with CNS lymphoma. The reported response rate of 43% is encouraging in the heavily pretreated population. Patients had received a median of five treatments prior to enrolling in this study including intravenous rituximab treatment. In addition, a synergistic effect of rituximab and methotrexate was seen, as evidenced by a rate of decline in CSF malignant lymphoma cells the day after combination therapy. Contrary to previous belief that the intra-parenchymal structures are poorly accessible via the intraventricular compartment, complete or partial responses also were seen in patients with primary parenchymal relapse. The study clearly met its primary objective and established prospectively that intraventricular immunochemotherapy is feasible and safe. However, a Phase 2 trial at the established dose level will be needed to confirm the efficacy of this regimen. In addition, despite excellent response rates, the majority of patients relapsed within 3 months suggesting development of resistance to rituximab. ■

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ILLUSTRATIVE CASE SERIES

Management of Early-Stage Common Bile Duct Cancer

By Samir Kanani, MD

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

A 52-year-old female presented with right flank pain, elevated bilirubin, and mild jaundice to her primary care physician. Endoscopic retrograde cholangiopancreatography demonstrated a common bile duct stricture just above the pancreatic head with a suggestion of neoplasia. A pancreaticoduodenectomy (Whipple) was performed and pathology revealed invasive, well-differentiated adenocarcinoma involving the full-thickness of the bile duct wall immediately adjacent to but not invading the pancreatic parenchyma. Final margins of excision were negative as were three adjacent lymph nodes (LNs) within the resected specimen. The pancreas itself demonstrated some focal pancreatic intraepithelial neoplasia, but without malignancy, and eight additional benign LNs were also noted. Appendix was removed and this was negative. A celiac LN also was removed and negative. Cholecystectomy was performed demonstrating acute cholecystitis and steatosis, but no additional evidence of malignancy. This was staged as a pathologic T2A N0 distal common bile duct adenocarcinoma. Imaging included a CT scan of the abdomen and pelvis, demonstrating no evidence of distant metastatic disease. Chest x-ray revealed no suspicious lesions. Postoperative recovery was unremarkable and she now presents for discussion of adjuvant therapy.

DISCUSSION

Cholangiocarcinomas are relatively rare tumors in the United States. The incidence is approximately 3000 cases per year. Although most cases are sporadic, a history of primary sclerosing cholangitis does increase the risk significantly. Most cholangiocarcinomas are perihilar in location, and 20-25% are found in the distal bile duct. The pathology is consistent with adenocarcinoma in more than 90% of cases. CA19-9 and CA-50 are often elevated. MIB-1 > 29% predicts for worse outcomes.[1]

Surgery has been shown to be the only curative treatment for cholangiocarcinomas. The case illustrated above is uncommon in that < 30% of cases are actually resected with negative margins. Distal bile duct tumors are more likely to be resectable and have a better survival when compared to hilar tumors.[2] Median survival is approximately 16 months for distal bile duct tumors and 11 months for proximal bile duct tumors. Long-term survival has been reported as high as 60% in distal bile duct carcinomas that are resected with negative margins.[3] LNs are positive in ~50% of patients at presentation, and signify worse prognosis. It appears that patients with 5+ LNs have significantly worse survival than patients with 1-4 LNs.[4]

The role of adjuvant radiotherapy and chemotherapy for cholangiocarcinoma is unclear. There are no prospective trials that include this patient population. A number of retrospective studies do show a benefit in adjuvant therapy, particularly in patients with an R1 resection. The largest retrospective series to date has included more than 300 patients in China. This study demonstrated a survival advantage in those patients who received adjuvant chemotherapy and radiotherapy.[5] There are, however, a number of other studies that do not show a clear advantage to postoperative radiotherapy in this setting, including studies from Johns Hopkins University and Thomas Jefferson University. These studies are fraught with the biases of retrospective studies. In my opinion, when a retrospective study demonstrates that the addition of adjuvant therapy either improves control or survival *or* demonstrates equivalence, then it is likely a benefit would be shown in a randomized trial. There must be a reason that a particular institution recommended adjuvant therapy in some patients and not other patients. That reason probably relates to adverse features in the patients who received adjuvant therapy. If you compare a worse cohort to a better cohort and the cohort that was supposed

to do worse actually did as well as the cohort that was supposed to do well as a result of adjuvant intervention, then the intervention is likely beneficial. The potential benefits of adjuvant radiotherapy in decreasing local failures must be weighed against the risks of gastric/duodenal ulceration and obstruction. Most of the studies to date quote outdated radiation techniques. The use of modern IMRT techniques can decrease this risk if appropriately applied. Studies that document patterns of failure point to a 20% risk of liver failures, justifying a discussion about chemotherapy.

In conclusion, the above case presents an interesting challenge. I believe her 5-year overall survival is likely to be greater than 50%. She does have a risk of local recurrence and distal failure that could potentially be decreased with the use of adjuvant therapy including chemotherapy and radiotherapy. I would recommend a discussion about the potential complications of therapy, and based on the patient's performance status and the details of her pathology report (margin status), I would offer adjuvant combined modality 5FU and radiotherapy similar to pancreatic cancer, with possible combination chemotherapy before or after combined chemoradiotherapy. One could make an argument to observe the patient based on a single-institution retrospective series that demonstrates distal bile duct tumors have a better prognosis. Although 5-year survivals of 50-60% are encouraging with surgery alone, there certainly is room for improvement. ■

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ABSTRACT & COMMENTARY

Post RT Adjuvant Cetuximab for Locally Advanced Oropharyngeal Cancer

By William B. Ershler, MD

SYNOPSIS: In a randomized, Phase 2 trial, weekly maintenance cetuximab for 12 weeks after concomitant definitive radiation therapy/cetuximab induction was associated with better disease-free survival at 1 year. However, by year 2, the local recurrence rate was the same for both treatment groups and overall survival was also no different. Toxicity was transiently and only mildly worse for those treated with the additional 3 months of cetuximab.

SOURCE: Mesia R, et al. Adjuvant therapy with cetuximab for locally advanced squamous cell carcinoma of the oropharynx: Results from a randomized, phase II prospective trial. *Ann Oncol* 2013;24:448-453.

Although there has been improvement in the management of squamous cell cancer of the head and neck (SCCHN), overall survival for those who present with locally advanced disease remains only slightly better than what it was 2 decades ago. To improve outcomes for such patients, effective new treatments with less toxicity are currently under investigation.

Cetuximab is a chimeric monoclonal antibody that binds to the extracellular domain of epidermal growth factor receptor (EGFR).[1] Concomitant cetuximab and radiotherapy (RT) has proven superior to RT alone in producing local control, and preclinical studies[2,3] would suggest that extending cetuximab after RT would enhance local control and possibly overall survival.

To this end, Mesia and colleagues throughout Spain conducted a randomized, Phase 2 trial to evaluate the efficacy and safety of cetuximab maintenance therapy following definitive RT with concomitant cetuximab in patients with oropharyngeal cancer.

For this, ninety-one patients with stage III–IV M0 oropharyngeal tumors were randomly assigned to treatment with accelerated concomitant boost RT (69.9 Gy) plus cetuximab (400 mg/m^2 as initial dose followed by 250 m/m^2 weekly for the duration of RT) or the same treatment with an additional 12 consecutive weeks of cetuximab (250 mg/m^2) maintenance therapy. Study enrollment occurred from November 2005 to July 2007. The primary endpoint was locoregional control (LRC) at 1 year. Secondary endpoints included LRC rates at 2 and 3 years, specific disease-free survival (SDFS), event-free survival (EFS), overall survival (OS), and the safety and toxicity of concomitant RT plus cetuximab followed by 12 additional weeks of cetuximab.

The treatment arms were evenly matched for all

important prognostic indicators including age, sex, performance score, stage, and site of primary tumor. Treatment compliance during the concomitant phase was high and similar in both groups. More than 85% of the patients received the planned dose of RT and cetuximab. Further, compliance during the adjuvant phase was also high, with 79% completing 10 or more weeks of weekly adjuvant treatments.

Adverse events during concomitant treatment were comparable between both treatment groups. Only one patient discontinued cetuximab because of a hypersensitivity reaction after the first infusion. Cetuximab was generally well tolerated; most adverse events were grade 1-2 and mainly included skin rash, mucositis, odynophagia, and asthenia. There were few episodes of grade 4 toxic effect: n = 4 with mucositis, n = 1 with toxic skin rash, and n = 1 with radiation dermatitis. Notably, the toxicity due to RT recovered similarly in patients receiving adjuvant cetuximab when compared to the non-adjuvant group. Only the recovery from mucositis (grade 1–2) was slower in the adjuvant treatment group. However, skin toxicity was increased during the adjuvant treatment, but was mild in the majority of cases with a clear tendency toward improvement with time.

LRC at 1 year was superior among patients in the experimental arm treated with cetuximab maintenance (59% vs 47%). However, LRC was similar between both arms after 2 years of follow-up as a result of increased locoregional recurrences after the first year in the maintenance group.

COMMENTARY

Twelve weeks of cetuximab maintenance therapy after concomitant cetuximab + RT in locally advanced oropharyngeal carcinoma is feasible and improves clinical outcomes measured at 1 year. However, the improvement is not maintained beyond that, with comparable survival at year 2. Thus, it appears that epidermal growth factor receptor blockade is insufficient to completely eliminate minimal residual disease.

Accordingly, novel strategies need to be developed incorporating agents such as cetuximab or other targeted therapies with cytotoxic chemotherapy administered either combined or in sequence with RT to eliminate resistant local residual as well as disseminated microscopic disease. Although maintenance therapy in the current study was not associated with greater toxicity, the addition of chemotherapy may prove challenging in this regard. ■

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ABSTRACT & COMMENTARY

Parenteral Iron for Cancer-Associated Anemia

By William B. Ershler, MD

SYNOPSIS: In an observational study conducted in Germany of more than 600 anemic cancer patients receiving parenteral iron (ferric carboxymaltose), hemoglobin levels were shown to rise significantly. The iron treatment was well tolerated. Randomized interventional studies are warranted to demonstrate efficacy in terms of physical function and quality of life and safety in this population.

SOURCE: Steinmetz T, et al. Clinical experience with ferric carboxymaltose in the treatment of cancer- and chemotherapy-associated anemia. *Ann Oncol* 2013;24:475-482.

Anemia is common in cancer patients for a number of reasons including iron deficiency, inflammation, and chemotherapy,[1] and its presence negatively influences performance, quality of life, and even the effectiveness of tumor-directed therapy.[2,3] In fact, iron deficiency even in the absence of anemia is associated with impaired physical function, weakness, and fatigue,[4,5] all of which have been demonstrated to improve with iron supplementation.[6,7]

Iron deficiency can be recognized as either an absolute deficiency in total iron stores (low serum iron and ferritin levels) or by a reduction in utilizable iron in an individual with adequate stores (low transferrin saturation). Inasmuch as ferritin is upregulated during inflammation, the reliance on this measure may be misleading in patients with malignancy.

Anemia associated with cancer and cancer

chemotherapy has been treated with erythropoiesis-stimulating agents (ESA) or red cell transfusions, but not infrequent adverse consequences have been reported and alternative approaches are under active investigation. In this light, intravenous iron, known to improve response to ESAs, may alone be an effective means of improving cancer-associated anemia, although the data on its use without coadministration of ESA are lacking. To address this, Steinmetz and colleagues evaluated effectiveness and tolerability of a commonly used (in Europe) parenteral iron preparation, ferric carboxymaltose (FCM), in the routine treatment of anemic cancer patients.

For the purposes of this observational review, data on 639 patients enrolled in 68 hematology/oncology practices throughout Germany were analyzed. Of the 639 patients, 619 received FCM at the oncologist's discretion, 420 had eligible baseline hemoglobin (Hb) measurements, and 364 had at least one follow-up Hb measurement. Data of transfused patients were censored from analysis before transfusion.

The median total iron dose was 1000 mg per patient (interquartile range 600-1500 mg). The median Hb increase was comparable in patients receiving FCM alone (1.4 g/dL [0.2-2.3 g/dL; n = 233]) or FCM + ESA (1.6 g/dL [0.7-2.4 g/dL; n = 46]). Patients with baseline Hb up to 11.0 g/dL and serum ferritin up to 500 ng/mL benefited from FCM treatment (stable Hb ≥ 11.0 g/dL). Also, patients with ferritin > 500 ng/mL but low transferrin saturation benefited from FCM treatment. FCM was well tolerated; 2.3% of patients reported putative drug-related adverse events and these were mainly gastrointestinal. Only one serious adverse drug reaction occurred and this was in a heavily pretreated man with a head/neck tumor and pulmonary metastases who experienced respiratory failure on the same day he received his second FCM injection.

COMMENTARY

Fatigue is a common occurrence among cancer patients, particularly those who are undergoing chemotherapy or radiation therapy. Although anemia is commonly observed, clinicians have been less aggressive about treating with ESAs or transfusion in patients with moderate anemia for fear of accelerating disease or shortening survival.[8,9]

Yet, there are studies now demonstrating efficacy of parenteral iron in improving hemoglobin levels and reducing transfusion requirements,[10,11] and this, with the current observational analysis indicating both safety and efficacy of such an approach on a larger scale and in a variety of practice settings, provides rationale for more extensive investigation. In this regard, an interventional trial in cancer patients with mild-to-moderate anemia in which outcomes other than hemoglobin level, such as physical function (e.g., 6-minute walk test) and quality of life, would be very instructive. ■

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ABSTRACT & COMMENTARY

'Off-target' Effects? The Role of Statins in Cancer Biology

By Robert L. Coleman, MD

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

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

SYNOPSIS: Statin use among cancer patients with diverse malignancies is associated with reduced cancer-related mortality. The mechanism is plausible since statins inhibit cholesterol synthesis, which reduces the pool of compounds necessary in cellular proliferation and maintenance of critical cellular functions, such as membrane integrity, signaling, protein synthesis, and cell cycle progression. Prospective clinical trials are warranted.

SOURCE: Nielsen SF, et al. Statin use and reduced cancer-related mortality. *N Engl J Med* 2012;367:1792-1802.

Cholesterol-reducing statin agents have been associated preclinically with cancer cell growth inhibition and metastases prevention. Given the ubiquitous use of statins in the general population for reduction in cardiovascular risk, the authors evaluated statin use in cancer patients for effects on cancer-specific mortality. They assessed mortality among patients from the entire Danish population who had received a diagnosis of cancer between 1995 and 2007, accompanied by a minimum follow-up of 2 years. Among patients 40 years of age or older, 18,721 had used statins regularly before the cancer diagnosis and 277,204 had never used statins.

Multivariable-adjusted hazard ratios for statin users, as compared with patients who had never used statins, were 0.85 (95% confidence interval [CI], 0.83-0.87) for death from any cause and 0.85 (95% CI, 0.82-0.87) for death from cancer. Adjusted hazard ratios for death from any cause according to the defined daily statin dose (the assumed average maintenance dose per day) were 0.82 (95% CI, 0.81-0.85) for a "low" dose (0.01-0.75 defined daily dose per day), 0.87 (95% CI, 0.83-0.89) for "average" dose (0.76-1.50 defined daily dose per day), and 0.87 (95% CI, 0.81-0.91) for "high" dose (> 1.50 defined daily dose per day); the corresponding hazard ratios for death from cancer were 0.83 (95% CI, 0.81-0.86), 0.87 (95% CI, 0.83-0.91), and 0.87 (95% CI, 0.81-0.92), respectively. The reduced cancer-related mortality among statin users as compared with those who had never used statins was observed for each of 13 cancer types. A nested case-control study matched statin cancer patients to three non-statin using cancer patients to control for changes in staging and cancer treatment. The effects were similar to the larger general population analysis. The authors concluded that statin use in patients with cancer is associated with reduced cancer-related mortality. Further study of mechanism and effect in prospective studies is warranted.

COMMENTARY

As a complement to last issue's commentary on the use of metformin and its effect on ovarian cancer mortality, we have this provocative report of statin use. To summarize, statin use was associated with reduced cancer-specific mortality across 13 different malignancies. The data were derived from a unique resource, the enviable National Registry of Patients, which has nearly unbelievable quality control within the Danish health care system. Lending credibility to the study's conclusions are the 98% capture of index cancers associated with nearly 100% complete follow-up and prescriptive practices over a 13-year period among the entire Danish population. Also, to confront changes in the cancer classifications, staging, and treatment over the study period, a nested 1:3 matched case-control study was also conducted. In that analysis, statin users with cancer were matched to three non-statin users with cancer controlling for cancer type, gender, age at diagnosis, and year of diagnosis. The consistency of effect in "all-cause" death and "cancer-specific" death in the two analyses provide legitimacy to the hypothesis that statin use in patients developing cancer may provide up to a 15% reduction in the cumulative risk of these events. This is bolstered by a credible link to the mechanism of action of the statins, which is to perturb cholesterol synthesis. As is recognized, cholesterol is a fundamental structural component of mammalian cell membranes and structures.

It is also critical to many cellular processes that govern proliferation, and in cancer cells, processes that are involved in tumor growth, invasion, and metastases.[1,2] In particular, the mevalonate pathway (cholesterol synthesis pathway) is up-regulated in P53 mutated cancers, where cholesterol metabolites serve as important signaling substrates promoting the malignant phenotype.[3] Statin use in preclinical experiments has been shown to inhibit cellular growth and metastases. There is also evidence that statins can block the P-glycoprotein pump, which serves as a mechanism of resistance to some chemotherapeutics.[4]

Since the sample is so large and homogeneous, the clinical impact may be trivial in some cancers and not easily extrapolated to other ethnic groups. In addition, the combination of statins (which are metabolized via intestinal and hepatic cytochrome P450 oxygenases) with chemotherapy needs to be carefully considered, as they may compete for metabolic clearance. Further, there are gaps in the analysis, such as the consideration of important cofactors (tobacco use, balance of screening/early detection practices, cholesterol levels) and the observed lack of a dose effect, which may suggest a minimal dose could be just as important to mortality reduction but with fewer side effects. Nevertheless, the results are thought-provoking and support more definitive clinical investigation into the role of statins

in cancer therapy and their effect on long-term survival. ■

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

Continuing Education Questions

1. The addition of rituximab to CHOP chemotherapy has consistently shown a decrease in the incidence of CNS relapse in patients with systemic non-Hodgkin's lymphoma.

a. True
b. False

2. Which of the following statements regarding distal bile duct tumors is false?

a. Distal bile duct tumors have a worse prognosis when compared to proximal bile duct tumors.
b. Distal bile duct tumors are less common than proximal bile duct tumors.
c. Surgery is imperative in the cure of distal bile duct tumors.
d. The benefit of adjuvant chemotherapy and radiotherapy is controversial.

3. Twelve weekly doses of cetuximab following initial concomitant RT/cetuximab when compared to concomitant RT/cetuximab without additional cetuximab was shown by Mesia and colleagues to:

a. improve overall survival at 36 months of follow-up.
b. reduce local recurrence at 12 months of follow-up.
c. produce significantly greater long-term mucositis.
d. All of the above.

4. The observational report of parenteral iron use in cancer patients in Germany supports the conclusion that:

a. treatment is associated with higher hemoglobin levels.
b. physical function is improved in those who were shown to have a rise in hemoglobin level.
c. quality of life is improved in those who were shown to have a rise in hemoglobin level.
d. physical function is improved by treatment in all recipients whether there was a rise in hemoglobin level or not.

5. What was the reason for the nested case-control study on statin use and cancer-related mortality?

a. To evaluate other agents that could affect cancer outcome
b. To control for tobacco use
c. To increase the sample size
d. To account for changes in treatment practices
e. To look at different endpoints that may be more relevant to prescriptive practices

[IN FUTURE ISSUES]

Sunitinib in Older Renal Cell Carcinoma Patients

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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When One Antihypertensive Med is Not Enough: Which Combination?

Source: Kato J, et al. *J Am Soc Hypertens* 2012;6:393-398.

THE ALLHAT TRIAL IS THE LARGEST HYPERtension clinical trial ever done, originally enrolling more than 42,000 individuals. That trial concluded that a thiazide diuretic (chlorthalidone) was at least as good as — and in some situations superior to — a calcium channel blocker ([CCB] amlodipine) or an angiotensin converting enzyme inhibitor ([ACE] lisinopril), and that an alpha blocker (doxazosin) was inferior to any of the three others.

But ALLHAT also demonstrated that only about 25% of hypertensives are able to maintain control on one medication. So, when one antihypertensive med is not enough, which combination should we choose?

The ACCOMPLISH trial was the first to address this question on a large-scale basis (n = 11,506) by directly comparing ACE/CCB (benazepril/amlodipine) with ACE/diuretic (benazepril/hydrochlorothiazide). In this trial, outcomes were superior for ACE/CCB.

Not everyone can tolerate an ACE, most commonly due to cough. Kato et al performed a clinical trial to compare in 58 hypertensive elderly patients (mean age, 72 years) the efficacy of an angiotensin receptor blocker (ARB)/CCB (mostly olmesartan/amlodipine) with ARB/diuretic (mostly olmesartan/indapamide).

At the conclusion of the trial, the ARB/CCB combination provided superior blood pressure reduction to ARB/diuretic. The diuretic used in ALLHAT was chlorthalidone, which is definitely more potent than hydrochlorothiazide; whether substitution of chlorthalidone for indapamide in this trial might have tipped the scales in another direction remains unknown. ■

Vitamin D for Osteoarthritis: NOT

Source: McAlindon T, et al. *JAMA* 2013; 309:155-162.

FOR A BURGEONING POPULATION OF BABYboomers who wish to continue being physically active despite advanced years, tools to provide symptomatic relief from osteoarthritis (OA) are valuable (e.g., topical and systemic NSAIDs, opioids, physical therapy), but disease-modification is really the "holy grail." At the current time, we do not possess any disease-modifying pharmacotherapy for OA.

Since vitamin D (VID) is an important player in bone health, might it influence symptoms or disease progression of OA? McAlindon et al performed a 2-year randomized, placebo-controlled trial of VID in subjects with symptomatic OA of the knee. VID dose was titrated from 2000 IU/d up to as much as 8000 IU/d, depending on attainment of a goal plasma VID level between 36-100 ng/mL. In this population of mostly Caucasian adults (mean age, 62 years) living in the Boston area, it is perhaps not surprising that baseline levels of VID averaged 22 ng/mL.

At the end of the trial, no effect (positive or negative) was seen from supplementation with VID on either OA symptoms or evidence of disease progression as measured by degree of cartilage loss. ■

Early Identification of COPD Exacerbations

Source: Yanez AM, et al. *Chest* 2012; 142:1524-1529.

ACUTE EXACERBATIONS OF CHRONIC OBstructive pulmonary disease (AECOPD) are consequential: 10% of patients admitted to the hospital die, 25% of those admitted to the ICU die, and the mortality rate in the year following an AE-COPD hospitalization for those who are discharged home is as high as 43%. Even after successful recovery from an AE-COPD, decrements in pulmonary function from pre-event status are noted that are not regained. Early identification of AE-COPD, with an intent-to-treat with minimum delay, might possibly alter the ominous natural history of AE-COPD.

Historically, it has been shown that the increasing dyspnea characteristic of AECOPD typically begins about 5 days before patients seek consultation from their clinician. For asthma, wider swings in variation between morning and evening peak flow rate herald an acute deterioration, even before patients are overtly symptomatic. In a similar vein of thought, the authors postulated that changes in respiratory rate would signal an impending AE-COPD.

Oxygen-dependent COPD patients (n = 89) were asked to monitor respiratory rate daily for 3 months. Monitoring of daily respiratory rate (DRR) was performed automatically by installing a monitoring device to the patients' oxygen delivery systems. Although respiratory rate was monitored at three different times each day, only the mean DRR rate was used for evaluation.

During 3 months of follow-up, 30 of

the 89 patients required hospitalization for AE-COPD. Baseline average DRR for the group as a whole was 16 breaths/minute; among the subgroup ultimately admitted for AE-COPD, baseline DRR was 15.2. In the 5 days prior to an AE-COPD admission, their DRR increased to 19.1, but no meaningful change in DRR was seen in patients not requiring hospital admission. DRR may provide a new window into early identification of AE-COPD. ■

CKD: Consistency of GFR and Albuminuria as Risk Predictors

Source: Hallan SI, et al. *JAMA* 2012;308: 2349-2360.

CLINICIANS HAVE BECOME INCREASINGLY aware of the disease burden associated with chronic kidney disease (CKD), especially since the routine inclusion of a calculated estimated glomerular filtration rate (eGFR) within metabolic profile testing. Promulgation of CKD stages by national organizations and encouragement of clinicians to consider referral of patients with CKD at an earlier stage (usually by CKD stage 3-B) has prompted the clinical community to address eGFR as well as the presence, absence, and severity of urinary albumin excretion on a more consistent basis. Because of inherent renal functional decline associated with increased age, accompanied by decrease in muscle mass that contributes to the generation of creatinine, some have questioned whether current stratification of CKD by eGFR, albuminuria, or both holds true throughout the lifespan.

Hallan et al performed a meta-analysis on data from more than 2 million individuals in Asia, Australasia, Europe, and North/South America to investigate whether eGFR and the presence of albuminuria remain consistently predictive of adverse outcomes.

Although at older ages the *absolute* risk imparted by CKD was greater than in younger folks (simply because a larger absolute number of older individuals die than younger individuals, whether or not they have CKD), overall, the hazard ratio (HR) for mortality decreased with increasing age. For example, at an eGFR of 45 mL/min, the HR for death (when compared to a normal eGFR) was 3.5 for persons ages 18-54, 2.2 for ages 55-64, and 1.35 for ages > 75 years. A similar relationship was noted for albuminuria.

Albuminuria and reduction in eGFR are associated with adverse outcomes throughout the lifespan, although the HR for risk appears to lessen as we age. ■

Changing Outcomes for Patients with Chronic Hepatitis C

Source: van der Meer AJ, et al. *JAMA* 2012;308:2584-2593.

CHRONIC HEPATITIS C (HEPC) HAS AN INcreased risk for liver cancer, end-stage liver disease, and all-cause mortality. Fortunately, current antiviral treatments for HEPc (e.g., ribavirin and interferon) are effective in the majority of subjects. As many as 80% of HEPc patients who complete a therapeutic course will obtain what is called a sustained virological response (SVR); that is, no detectible HEPc virus 6 months *after* completion of therapy. SVR might reasonably be titled "cure," since indications are that absence of virus at 6 months is indicative of permanent eradication.

Nonetheless, some patients enjoying SVR already have experienced inflammatory hepatic changes resulting in fibrosis. It has not been sufficiently elucidated whether achievement of SVR ultimately reduces risk for mortality, liver cancer, or hepatic failure, especially in a group with already established hepatic fibrosis.

Using an international multicenter database (n = 540), the outcomes of HEPc patients with long-term follow-up (mean 8.4 years), as well as biopsy-proven fibrosis, were investigated to compare those who attained SVR vs those who did not. The mortality rate was essentially three times greater in those who did not attain SVR (26% vs 8.9%); the comparative cumulative incidence rate of liver-related mortality or transplantation was even more dramatic: 1.9% (SVR) vs 27.4% (SVR not attained). The attainment of SVR is associated with substantial long-term reductions in mortality as well as less need for liver transplantation. ■

Is Fructose a Primary Culprit in Obesity?

Source: Page KA, et al. *JAMA* 2013;309: 63-70.

SORTING OUT THE CAUSES OF THE CURRENT pandemic of obesity has not been easy and appears to have contributions from various life quadrants: activity, genetics, absolute calorie ingestion, and — most recently — characteristics of the calories we ingest. For instance, whereas in the recent past one might simplistically think that a gram of ice cream and a gram of broccoli should result in similar metabolic impact, recognition of the glycemic index (variation in glucose rate of absorption from different food sources) has taught us that a calorie is not necessarily always a calorie in the grander scope of things.

Fructose, an increasingly commonplace component of fast foods, snacks, etc., has recently come under fire as a potential culprit exacerbating the obesity pandemic. Mechanistically, fructose could be metabolically detrimental because (compared to glucose, that is) it blunts satiety-inducing GLP-1, and fails to shut off appetite-stimulating ghrelin.

Page et al measured regional cerebral blood flow in response to glucose and fructose ingestion. They found that fructose did not produce the same reduction in hypothalamic cerebral blood flow (associated with satiety and fullness) as did glucose. Disproportionate consumption of fructose may be a significant contributor to weight management problems. ■

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Aspirin Use and Age-Related Macular Degeneration

In this issue: Aspirin use and AMD risk; using NSAIDs and antihypertensive agents; and FDA actions.

Does aspirin cause AMD?

Does regular aspirin use put patients at risk for age-related macular degeneration (AMD)? That is the finding in a highly publicized study from Australia published in *JAMA Internal Medicine* (formerly *Archives of Internal Medicine*). A prospective analysis was conducted from an Australian population-based cohort that included four examinations in 15 years as well as questionnaires regarding aspirin use. Of the 2389 participants with follow-up available, 257 (10.8%) were regular aspirin users and 63 of these (24.5%) developed neovascular (wet) AMD. Regular aspirin users were more likely to develop neovascular AMD: The 15-year cumulative incidence was 9.3% in aspirin users and 3.7% in non-users. After adjustment for age and multiple cardiovascular risk factors, regular users of aspirin had an odds ratio of neovascular AMD of 2.46 (95% confidence interval [CI], 1.25-4.83). The association showed a dose response effect, with daily users at higher risk. Aspirin was not associated with geographic atrophy (dry AMD). The authors conclude that "regular aspirin use is associated with increased risk of incident neovascular AMD independent of a history of cardiovascular disease and smoking." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.1583). A related editorial points out that age-related AMD is the leading cause of blindness in Western countries, and this study suggests that regular aspirin is associated with an approximate 2.5-fold greater risk in incident AMD. The study is not a randomized trial, and although there is some biological plausibility in the association between aspirin use and development of AMD, this study is "not sufficiently robust to be clinically directive." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.2530.) The take-home message for now is that for patients who are likely to benefit from aspirin (secondary prevention of cardiovascular disease), practice should not change. However, for those patients who take aspirin for indications that are less compelling, we may want to rethink the recommendation until good trials on the relationship between aspirin use and AMD can be assessed. ■

NSAIDs and antihypertensive agents

Mixing certain antihypertensive agents with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of renal failure, according to a new study. In a retrospective cohort study of nearly 500,000 users of antihypertensive drugs in the United Kingdom, rate ratios of acute kidney injury associated with current use of certain antihypertensive agents with NSAIDs were assessed. After a mean follow-up of 5.9 years, 2215 cases of acute kidney injury were identified. Overall, current use of a single antihypertensive (either diuretics, angiotensin-converting enzyme inhibi-

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tors [ACEIs], or angiotensin receptor blockers [ARBs]), along with an NSAID was not associated with increased rate of acute injury. However, combining a diuretic with either an ACEI or ARB along with an NSAID increased the rate of acute kidney injury significantly (rate ratio 1.31, 95% CI, 1.12-1.53). This 31% increased risk of acute kidney injury was driven by a nearly two-fold increased risk in the first 30 days of use. The authors conclude that triple therapy consisting of diuretics with an ACEI or ARB along with an NSAID was associated with an increased risk of acute kidney injury, especially at the start of treatment (*BMJ* published online January 8, 2013. doi.org/10.1136/bmj.e8713). ■

FDA actions

An advisory committee to the FDA has recommended moving hydrocodone/acetaminophen (Vicodin, Norco) from schedule III to schedule II later this year. The move would put the drug in the same category as morphine and oxycontin, and would require a handwritten, tamper-proof prescription for every prescription and refill. Vicodin — the most widely prescribed drug in this country — is at the center of the controversy regarding prescription drug abuse, which has become "epidemic" in this country, according to the CDC. The United States consumes 99% of all the hydrocodone produced worldwide, and deaths attributable to prescription opioid abuse skyrocketed in the last 2 years, outpacing deaths from illegal opioid drugs, including heroin. The move is supported by some advocacy groups, including an endorsement by the American Academy of Pain Medicine, but not by others. Some physicians are concerned that the schedule change will be a major inconvenience for legitimate pain patients and their physicians, who will be required to write a tamper-proof prescription for each refill of the drug.

The FDA has approved an over-the-counter version of topical oxybutynin for the treatment of overactive bladder in women ages 18 and older. The approval is for women only, with oxybutynin available to men by prescription only. The anticholinergic drug has been used for years by prescription for this indication. In studies of more than 5000 subjects, it was determined that consumers can understand the labeling and "properly select whether the product is right for them." Merck will market the product as a patch that is replaced every 4 days under the trade name Oxytrol for Women.

The FDA has lowered the recommended doses for zolpidem (Ambien) for women. The agency based its recommendation on findings that the popular insomnia drug might impair alertness the next morning if taken at recommended doses. The recommendation is also based on findings that zolpidem stays in the body longer than previously thought, especially in women who process the drug somewhat slower. The new recommended maximal dose for women has been lowered from 10 mg to 5 mg for the immediate-release product, and from 12.5 mg to 6.25 mg for the extended-release (Ambien CR). The FDA further recommends that zolpidem and all insomnia drugs should be used at the lowest dose needed to treat symptoms in both men and woman.

The FDA has approved alogliptin for the treatment of type 2 diabetes. The drug is the fourth dipeptidyl peptidase-4 inhibitor after sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Tradjenta). Takeda Pharmaceuticals has been seeking approval for more than 5 years, dealing with the FDA's tighter standards for new diabetes drugs. The approval was based on 14 trials involving about 8500 patients as well as five ongoing postmarketing trials. The agency also approved two additional combinations of alogliptin with metformin and pioglitazone. Alogliptin alone will be marketed as Nesina, alogliptin/metformin will be marketed as Kazano, and alogliptin/pioglitazone will be marketed as Oseni. Both combination products carry boxed warnings (for lactic acidosis associated with metformin and heart failure associated with pioglitazone). All three are distributed by Takeda Pharmaceuticals.

Johnson & Johnson is one step closer to approval of canagliflozin, the first of a new type of diabetes drug. The Endocrionologic and Metabolic Drugs Advisory Committee voted 10 to 5 in favor of approving the drug while still expressing some concern about the cardiovascular safety of the agent. Canagliflozin is an oral inhibitor of the sodium glucose cotransporter 2 (SGLT2) that reduces reabsorption of glucose in the kidney, resulting in increased urinary glucose excretion with a consequent lowering of plasma glucose levels as well as weight loss. If eventually approved by the FDA, it would be the first SGLT2 inhibitor on the U.S. market. The FDA denied a similar drug 1 year ago (dapagliflozin) because of increased risk of bladder and breast cancer. The favorable vote was based on clinical trials of more than 10,000 patients worldwide which showed that the drug improves blood sugar levels and led to modest weight loss as well as reduction in blood pressure. ■