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Clinical Oncology [ALERT]

A monthly update of developments in cancer treatment and research

Beginning with this month's issue, we are spotlighting a new case series that involves a guest oncologist reviewing a pertinent case study in the field, a new round-up section featuring an expert in a particular specialty of oncology, and a fresh new look for the publication.

ILLUSTRATIVE CASE SERIES

RENAL CELL CARCINOMA: A REVOLUTION IN MOLECULARLY TARGETED THERAPY

Guest Discussant: Robert Fenton, MD, PhD
Clinical Associate Professor, Clinical Research Committee Member, University of Maryland, Marlene and Stewart Greenebaum Cancer Center
Dr. Fenton reports no financial relationship relevant to this field of study.

CASE HISTORY AND INITIAL EVALUATION

A 52-year-old male presented to his primary care physician in February 2006, complaining of decreasing exercise endurance. The patient was a runner, and typically ran 5-8 miles three or four times a week. During the past month, he noted difficulty in completing the longer runs, and initially attributed this to a persistent cold and URI. The patient's PMH was unremarkable, and he was taking no medications. He had a colonoscopy when he turned 50 years old, which was negative. His mother was alive, with some osteoarthritis and hypertension, and his father died from coronary artery disease. His two sisters were both alive and well. The patient is a retired Army major who currently teaches aerospace engineering at the local university. He is married with two children, both in college. Review of symptoms was notable for a lack of weight loss or other constitutional symptom, his appetite was excellent, and he denied cough, chest pain, neurologic symptoms, blood in stool or urine, arthritis, or muscle pain. On physical exam, the heart rate was 60, BP 110/70, respiratory rate 10, O_2 saturation 99%, and he was afebrile. Physical exam was completely normal. Laboratory studies showed a normal metabolic panel, with creatinine of 1.1 and normal LFTs. His CBC was remarkable, with a hemoglobin level of 10.5 g/dL, hematocrit of 31%, 245,000 platelets, and a WBC of 5.2, with a normal differential. The MCV was 77 fL. A urinalysis demonstrated TNTC RBC.

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DIAGNOSIS AND SURGERY: ROLE OF ADJUVANT THERAPY IN RCC

The patient's exertional dyspnea was almost certainly due to microcytic anemia, and the likely cause was bleeding from somewhere in the urinary system. The patient was referred to a urologist, who performed a cystoscopic exam that showed a normal bladder, suggesti ng that the bleeding was arising from higher up. A CT scan was performed with IV contrast. This demonstrated a 9 cm mass in the upper pole of the left kidney that abutted the renal pelvis, but appeared to be confined to the kidney. There was no evidence for invasion of the renal vein or IVC, and a few regional LN were slightly enlarged (1-1.5 cm diameter). Chest and head CT and a bone scan were negative for metastatic renal cell carcinoma (RCC). The patient was taken to the OR, and a left radical nephrectomy was performed. The primary tumor measured 9 x 7 x 6 cm, was centrally necrotic and highly vascular, and extended into the perinephric fat but not into Gerota's fascia. There was no invasion into the renal vein. Five perinephric LN were removed, and all were negative. Histology showed this to be a clear-cell tumor, pathologic grade 2. The final diagnosis was clear-cell RCC, T3N0M0, stage 3. The patient made an unremarkable recovery from surgery, with correction of his anemia. In discussions with his oncologist, he was informed that his chances of relapse were as high at 50%, but that there was no evidence that adjuvant treatment would significantly lower this risk, as a number of randomized studies with IFNa and/or IL-2 had failed to demonstrate a reduction in disease recurrence.[1,2] There were no compelling adjuvant clinical trials available for this patient in 2006.

FIRST-LINE THERAPY IN RCC PATIENTS WITH EXCELLENT PERFORMANCE STATUS

The patient was asymptomatic until March 2007, when he developed a chronic cough that did not respond to azithromycin. CT scan of the chest demonstrated 10 pulmonary nodules, all 1-2 cm in diameter scattered throughout both lung fields. CT of the abdomen and head, and a bone scan, were negative. Given that the patient's performance status was 90%, he was referred to the local university for consideration of high dose IL-2 therapy. The patient was told that for good-prognosis patients (KPS > 80, disease-free interval >1 year, no hypercalcemia, increased LDH, or anemia) with lung metastases only, there was a 10% chance of long-term, disease-free survival.[3,4] He received 14 doses of IL-2 at 600,000 IU/kg q8h, and left the hospital after one week. After a 10-day break, he was admitted for more high-dose IL-2, receiving only 11 doses due to hypotension, capillary leak-induced pulmonary edema, and a creatinine of 6. He made a full recovery after cessation of IL-2. He received two more courses of this treatment, and follow-up CT scans revealed a complete resolution of all pulmonary disease. The patient refused a final cycle of IL-2, and he was followed for recurrence with q3 month CT scans.

VEGF-PATHWAY INHIBITORS IN RCC: CONCEPT OF ONCOGENE ADDICTION

In November 2008, CT scans showed recurrence of bilateral pulmonary nodules and the development of enlarged para-aortic LN just above the level of the right renal artery. The patient complained of mild low-back pain, but his KPS was 90%. The patient was educated about a new class of drugs, the tyrosine kinase inhibitors (TKI), which demonstrated antitumor benefit in randomized, Phase-III trials. These were sorafenib and sunitinib, oral small-molecule inhibitors of tyrosine kinases that prevented tumor growth by blocking angiogenesis through inhibition of the vascular endothelial growth factor (VEGF) receptors. Unlike bevacizumab, which binds to the ligand VEGF, these competed with ATP binding in the active site of the kinase, blocking phosphorylation of downstream targets. Due to the inactivation of the von Hippel Landau gene in 90% of clear-cell tumors (by genetic or epigenetic silencing), the transcription factor HIF-1 is up-regulated, inducing the constitutive transcription of VEGF and other genes normally activated in response to hypoxia and nutrient deprivation.[5,6] Sorafenib, a broad-spectrum inhibitor of VEGFR, platelet-derived growth factor (PDGF) receptor, FMS-like tyrosine kinase (FLT)-3, fibroblast growth factor (FGF) receptor-1, and the serine/threonine kinase Raf, demonstrated activity in the Phase-III TARGET trial of previously treated stage-IV RCC patients. Compared to placebo, patients receiving Sorafenib (400 mg po BID) had a PFS of 5.5 vs. 2.8 mo (HR 0.44), and OS of 17.8 vs. 15.2, which was not significant due to the crossover design of the study.[7] Importantly, sorafenib was as effective in patients older

than age 70, without increased toxicity.[8] Interestingly, in a randomized, Phase-II study of previously untreated patients, sorafenib did not show any improvement over IFNa.[9] Sunitinib, with activity directed against VEGFR, platelet-derived growth factor receptor (PDBFR), and c-KIT (the receptor for stem cell factor), demonstrated increased activity as first-line treatment when compared to IFNa, with an overall response rate of 39% vs. 8%, PFS advantage of 11 vs. 5 mo (HR 0.54), and a significant OS benefit of 26.4 vs. 21.8 mo.[10]

Because the patient had received cytokine therapy, it was elected to treat him in the second-line therapy with sorafenib, 400 mg PO BID. After 14 days of treatment, the patient was seen in the clinic complaining of localized erythema at pressure points of his fingers and the soles and proximal MTP of his feet, which had become so symptomatic that walking was quite painful. The painful areas were marked by circumscribed regions of hyperkeratosis, consistent with a diagnosis of sorafenib-induced hand-foot syndrome, grade 2. The patient was instructed to avoid touching hot water or surfaces, to use padded running shoes, and to apply urea cream gently to the affected areas of his hands and feet twice a day. The sorafenib dose was lowered to 400 mg once a day for 7 days, during which time the toxicity resolved to grade 1. He was then restarted on the BID schedule, continuing the supportive care to hands and feet, with ultimate slow resolution of the hand-foot symptoms over the next few months. CT scans taken at two-month intervals demonstrated a small decrease in diameter of most of the pulmonary lesions and LN without reaching partial response criteria; there was no evidence of tumor growth and no new lesions. The patient complained of mild fatigue (grade 1) and had an increase in blood pressure that did not require treatment. There was no diarrhea or myelosuppression.

mTOR INHIBITORS IN FIRST-LINE OR SUBSEQUENT TREATMENT OF RCC

The patient did well with stable disease until October 2009, when his pulmonary lesions progressed and he developed two new 3 cm liver metastases. Bone scan and head CT remained negative. A discussion was held with the patient. One option was to change treatment to another therapy targeting the VEGF-pathway. This could be sunitinib, or the recently FDA-approved agent pazopanib, which has a spectrum of activity and efficacy similar to sunitinib, but appears to be more tolerable (e.g., less fatigue).[11] However, there is currently little data for the use of further VEGF-targeted therapy after Sorafenib failure. In principle, if his tumor had become refractory to VEGF-pathway inhibition, it would be more efficacious to target a distinct signaling pathway that was required by tumor cells for survival and/or proliferation. Recent clinical studies have demonstrated an important role for the PI3K/Akt/mTOR pathway in RCC, and Phase-III trials have demonstrated the efficacy of the mTOR inhibitors temsirolimus and everolimus in first- and second-line therapies, respectively. mTOR is a protein kinase that regulates cellular protein translation by sensing nutrient availability. By phosphorylating p70S6K and 4E-BP1, it promotes the translation of specific classes of mRNA, including the mRNA encoding HIF-1.[12] Hence, inhibiting mTOR can have anti-angiogenic activity by indirectly blocking VEGF production, but can also have direct effects on tumor cell metabolism. In a Phase-III study of previously untreated poor-prognosis RCC patients, temsirolimus (given IV at 25 mg/week) demonstrated a PFS advantage of 5.5 vs. 3.1 mo compared to IFNa, and a significant increase in OS from 10.9 to 7.3 mo.[13] Toxicities included rash, mucositis, asthenia, nausea, hyperglycemia, anemia, and rare hypersensitivity reactions. Everolimus was tested in patients who had progressed on sunitinib or sorafenib and, in a placebo- controlled, randomized study, demonstrated a PFS advantage of 4.0 vs. 1.9 mo (HR 0.3), with 63 vs. 32% SD, and 1% vs. 0% responses, demonstrating the tumor-static nature of this class of agents.[14] Toxicities included lymphopenia, hyperglycemia, hyperlipidemia, stomatitis, and rare pneumonitis. Temsirolimus and everolimus were FDA-approved for treatment in the first line for poor-risk patients and after failure of VEGF-targeted therapies, respectively. With the Phase-III data in mind, this patient was treated with everolimus, receiving 10 mg PO qd. He tolerated this well, with only grade 2 hyperglycemia treated with glypizide. In January 2010, CT scans demonstrated that the patient's pulmonary and LN metastases, which had progressed on sorafenib, were now stable, without evidence of new lesions. He remains on everolimus and is working full-time with a KPS of 90%. He continued to run during all his outpatient treatments, although he now runs "only" about 10 miles a week.

[The patient did well with stable disease until October 2009, when his pulmonary lesions progressed and he developed two new 3 cm liver metastases.]

KEY CONCEPTS AND FUTURE CLINICAL RESEARCH: FROM RAGS TO RICHES IN RCC

1. High-dose IL-2 is the only RCC therapy with a potential for cure. However, this is limited to a highly select subset of RCC patients.
2. VEGF-targeted pathways are effective, as they target the oncogene addition of RCC caused by loss of the VHL gene product and constitutive activation of the HIF-1/

VEGF axis. Multiple VEGF pathway-targeted agents are now FDA-approved (sunitinib, sorafenib, bevacizumab, pazopanib), with others in the pipeline (e.g. axitinib, which has more potent anti-VEGFR activity). Clinical trials will be needed to determine which agent to use in different settings and whether OS can be extended through rational, sequential use of these agents. Combining agents from within this group ("vertical blockade") has been attempted and appears to be very toxic.

3. mTOR inhibitors provide a second molecular target for use in the first-line setting or after progression on VEGF-targeted therapies. Again, the choice of agent, and how to best sequence these with VEGF-targeted therapies to improve OS while maintaining QOL, will be the subject of ongoing and future clinical trials.

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RAPID REVIEW

Multiple Myeloma

Guest Discussant: Robert Fenton, MD, PhD

Myeloma patients with symptoms caused by the disease (i.e., anemia, lytic bone lesions, hypercalcemia, renal insufficiency, extramedullary plasmacytoma) require treatment with chemotherapy. Autologous stem cell transplant (ASCT) is still considered a standard of care for non-high-risk MM patients below the age of 70, as it prolongs event-free survival and overall survival compared with standard chemotherapy.[1,2] This concept is under scrutiny, as "standard chemotherapy" now includes new agents such as thalidomide, lenalidomide, and bortezomib, which have potent myeloma activity when used alone or when combined with chemotherapeutic agents with known activity against MM (e.g., melphalan, cyclophosphamide, doxorubicin, steroids). Important decisions concerning the use of ASCT in MM include:

1. **Who to transplant?** Patients with poor risk features, such as those with deletion of chromosome 13 or hypodiploidy on routine cytogenetic analysis; those with t(4;14), t(14;16), or 17p- by FISH; or a plasma cell labeling index 3 define a subgroup of 25% of MM patients with a median survival of less than two years following ASCT.[3] These patients should receive treatment with a regimen that includes bortezomib (which appears to overcome many poor-risk cytogenetic features), preferably on a clinical trial, and possibly followed by an allogeneic stem cell transplant for appropriate candidates. ASCT for standard-risk patients is generally excluded for those older than 75 years (depending on physiologic age), BR > 2 mg/dL, creatinine > 2.5 mg/dL, ECOG PS >2, and NYHA CHF level 3 or 4 due to the increased likelihood of severe toxicity.

2. What induction chemotherapy to use? Lenalidomide (25 mg/m^2 PO d1-21 of a 28-day cycle) plus low-dose dexamethasone (40 mg PO at the start of each week) is the preferred induction therapy for standard-risk patients (those with no high-risk features). This regimen has a high overall response rate, and the one-year overall survival is higher with the low-dose dexamethasone regimen.[4,5] An alternative is

the combination of thalidomide with dexamethasone, which is associated with an increased risk of thromboembolic complications (even after prophylaxis) and a lower response rate in untreated patients. For patients with poor-risk myeloma, who have rapid progression after ASCT, there are accumulating data that bortezomib can overcome poor cytogenetic features when used in combination with standard chemotherapy or in more elaborate transplant regimens.[6,7] It is likely that new regimens containing bortezomib and other highly active myeloma therapeutics such as lenalidomide, thalidomide, liposomal doxorubicin, melphalan, and dexamethasone or prednisone will yield higher rates of CR than currently attainable. Such combinations, initially investigated in poor-risk patients, may be moved up-front for use in standard-risk patients, with ASCT being used as consolidation therapy. Furthermore, it will be important to determine if upfront combinations of active agents will prolong survival compared to withholding their use until relapse after ASCT.

3. When to transplant? Stem cells are usually collected after 2-4 cycles of induction therapy. This treatment should reduce the MM burden of the BM and peripheral blood without damaging hematopoietic stem cells and preventing adequate collection of sufficient stem cells for two transplants (e.g. > 6 x 106 CD34+ cells, to be used for tandem transplant).[8] Mobilization with cytoxan and G-CSF may be required after lenalidomide-based induction, although the role of plerixafor (AMD3100, an inhibitor or chemokine receptor 4) is being studied.[9] SCT is usually performed 2-4 weeks after stem cell harvest, although data indicate that delaying ASCT until resistance develops to standard chemotherapy does not significantly affect OS, although early SCT is associated with a better QOL and event-free survival.[10]

4. Which patients should receive a tandem transplant? Meta-analysis of six randomized, controlled trials of single vs. double HSCT did not demonstrate a survival benefit for tandem transplant; however, data indicated an increase in OS for the subgroup of patients that do not achieve either a CR or very-good partial response (VGPR) from the first transplant.[11] Until data from new studies indicate otherwise, tandem transplant is a reasonable choice for patients with less then a VGPR after the initial transplant, with the second transplant given within six months of the first.[12] For patients with CR or VGPR after one ASCT, stem cells can be stored and used at the time of relapse.[13]

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ABSTRACT & COMMENTARY

Rate and Significance of Persistent Cytopenia after Fludarabine-Combination Chemotherapy

By William B. Ershler, MD

SYNOPSIS: In a cohort of 61 patients treated with frontline fludarabine combination chemotherapy for CLL or low-grade lymphoma, 43% experienced cytopenias for three or more months after completion of therapy. The median time to recovery for this group was between 7-10 months, and complications (e.g., infection, transfusions) were more common. Explanation for the persistent cytopenias remain unclear, but it does not appear to be the result of a greater propensity for residual or aggressive disease as features of such were seen equally in those with and without persistent cytopenias.

SOURCE: GILL S, ET AL. THE FREQUENCY, MANIFESTATIONS, AND DURATION OF PROLONGED CYTOPENIAS AFTER FIRST-LINE FLUDARABINE COMBINATION CHEMOTHERAPY. *ANN ONCOLOGY.* 2010;21:331-334.

Fludarabine-based combination chemotherapy, with or without added rituximab, has become established treatment for patients with low-grade lymphomas and chronic lymphocytic leukemia. Although, generally, combinations that include cyclophosphamide and/or mitoxantrone have been well tolerated, hematological toxicity is frequently observed, including protracted cytopenias, impaired mobilization of peripheral blood progenitor cells, and the development of myelodysplasia.[1-3] Despite the common use of fludarabine combinations, the rate of development and clinical consequences of treatment-related prolonged cytopenias has not been clearly established.

To address this, Gill et al at the Peter MacCallum Cancer Centre in Victoria, Australia, performed a retrospective analysis of patients with lymphoma or CLL treated at their institution with a fludarabine combination as their first cytotoxic therapy over a 12-year period (1996-2007). Typically, patients were treated with fludarabine (25 mg/m^2) and cyclophosphaminde (250 mg/m^2) intravenously for three days, every 28 days.

The primary endpoint of the analysis was the rate of cytopenias present at three months and beyond after the final cycle of chemotherapy. This was defined as at least two measurements below the lower limit of the reference range at their laboratory for hemoglobin (Hb, <13 g/dL for men < 65 years or 12.5 g/dL for men > 65 years, < 11.5 for women < 65 years or < 11 g/dL for women > 65 years), absolute neutrophil count (ANC = 2000/uL) and platelet count = 140K/uL. Alternative causes of cytopenias (i.e., other than chemotherapy) were excluded by bone marrow assessment and by examination of patient records for the presence of possible causative medicines, nutritional deficiencies, or the presence of persisting splenomegaly.

Sixty-one patients receiving initial therapy with fludarabine-based regimens were categorized according to the presence of post-treatment cytopenias based upon the data available. Cytopenias, unrelated to residual disease, persisting three months after completion of chemotherapy, were found in 43% of patients. Cytopenias were associated with clinically important rates of infection and transfusion requirement (p = 0.03), and predicted for worse overall survival (61% vs. 96% at 60 months, p = 0.05). Increasing age predicted for persistent cytopenias (p = 0.02), but the presence of pretreatment cytopenias and delivered-dose intensity were not predictive. The median times to resolution of anemia, neutropenia, and thrombocytopenia were 7, 9, and 10 months, respectively.

During the first six months after therapy, the overall complication rate (including infection and transfusion requirement) was significantly higher for those who had protracted cytopenias compared with those who did not. Treatment-related myelodysplastic syndrome/acute myeloid leukemia (AML) developed in three of the patients with (at 12, 40, and 94 months), and one patient without (at 8 months), persistent cytopenias. The overall survival at 60 months was 61% for patients with persistent post-treatment cytopenias and 96% for those patients without. Yet, need to retreat lymphoid malignancy was not different in the two groups (27% for those with persistent cytopenias and 23% for those without).

COMMENTARY

Thus, cytopenias often persist > 3 months after first-line fludarabine-combination therapy and can lead to important clinical sequelae. Although cytopenias generally resolve over time, treating physicians should be aware of these factors when considering fludarabine-combination chemotherapy and when documenting treatment-response status in chronic lymphocytic leukemia.

Of the many factors that one might predict would result in persistent cytopenias, only age was found to be significant.

Others, including underlying disease, marrow involvement before therapy, and presence of pre-treatment cytopenias, were not found to be predictive. Furthermore, treatment-related factors such as the number of cycles administered, requirements for dose reduction or delay, and the addition of rituximab were not found to have any association with the incidence of cytopenias.

It is notable that current guidelines for documenting persistent disease after treatment for CLL include the presence of cytopenias,[4] and the findings from the current report would suggest that prior fludarabine-combination chemotherapy should be taken into consideration before the persistent cytopenias three months after therapy are ascribed to residual or advancing CLL.

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ABSTRACT & COMMENTARY

Pelvic Fracture as a Consequence of Radiation for Cervical Cancer

By William B. Ershler, MD

SYNOPSIS: Among 300 women treated at MD Anderson with radiation therapy for cervical cancer, pelvic fracture occurred in 29, with 83% diagnosed within two years of completing therapy. Older age and lower BMI were found to be significant risk factors.

SOURCE: SCHMELER KM, ET AL. PELVIC FRACTURES AFTER RADIOTHERAPY FOR CERVICAL CANCER. IMPLICATIONS FOR SURVIVORS. *CANCER*. 2010;116:625–630.

Curative treatment for cervical cancer often calls for radiation therapy, either delivered primarily or as an adjunct to surgical excision and chemotherapy.[1,2] With the improvement in survival that such therapies have provided, there are now concerns over the long-term consequences of such approaches. Among these is the occurrence of pelvic fractures in those patients who had received radiotherapy. To address the incidence and risk of pelvic fracture among treated cervical-cancer patients, Schmeler et al at MD Anderson performed a retrospective review of the case histories of women treated there in the years 2001 through 2006.

Of the 516 women treated with curative-intent radiotherapy, 300 patients had at least one post-treatment computed tomography scan or magnetic resonance imaging study available for review, and they comprised the study population. All imaging studies were reviewed by a single radiologist to evaluate for fractures.

Pelvic fractures were noted in 29 of 300 patients (9.7%). Fracture sites included sacrum (n = 24; 83%), sacrum and pubis (n = 3; 10%), iliac crest (n = 1; 3%), and sacrum and acetabulum (n = 1; 3%). Only thirteen of the thirty patients (45%) were symptomatic, with pain being the most common presenting symptom. The median time from the completion of radiotherapy to the detection of fractures on imaging studies was 14.1 months (range, 2.1-63.1 months), with 38% of patients diagnosed within one year and 83% diagnosed within two years of completing therapy. The median age of the patients at diagnosis was higher in the women who developed a fracture compared with the women who did not (56.5 years vs. 46.7 years; $p = .04$). A higher number of women with a fracture were postmenopausal (62% vs. 37%; $p = .03$). The median body mass index was lower in the women who had a fracture (26.0 kg/m^2 vs. 28.0 kg/m^2; $p = .03$).

COMMENTARY

Thus, pelvic fractures were detected in approximately 10% of women after radiotherapy for cervical cancer. This, itself, is not a new finding, as there have been reports of an increased risk of increased pelvic fracture among women who received radiation for gynecological malignancy.[3-5] However, unlike prior reports, this review included primarily American women and is large

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enough to establish risk factors. Thus, it was found that older patients and those with larger BMI were statistically more likely to sustain pelvic fracture. There were no statistically significant differences found with regard to ethnicity, smoking history, stage of disease, tumor grade, radiation dose, or use of concomitant chemotherapy between those who did or did not sustain fracture.

Among this cohort, the majority of fractures were diagnosed within two years of completion of treatment, although the median follow-up was only 20, and there were fractures observed in some after 60 months.

Although by no means established, it appears that radiation negatively affects the bone remodeling process, resulting in osteopenia and fracture risk. With an apparent risk of fracture not long after the completion of therapy, it is reasonable to develop strategies to enhance bone health for these patients. Certainly, bone mineral density screening and pharmacologic intervention are reasonable precautions and should be the subject of future investigation.

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CME Questions

9. Which of the following factors are associated with increased risk of sustaining pelvic fracture in women treated with radiation therapy for cervical cancer?

a. Age 60 years or older
b. Cigarette habit
c. Obesity
d. a and b
e. a and c

10. For patients with CLL treated with fludarabine-based combination chemotherapy, which of the following factors correlate with persistent cytopenias observed 3 months after completion of treatment?

a. Patient age
b. Presence of pretreatment cytopenias
c. Pretreatment marrow involvement
d. Two or more dose-delays during treatment phase
e. All of the above

11. Autologous stem-cell transplant for patients with multiple myeloma should be considered:

a. in the strategy for first-line treatment.
b. for patients who have relapsed after allogeneic transplant.
c. for patients only after they have relapsed from a lenalidomide or other first-line chemotherapy regimen.
d. only under the auspices of clinical trial.

Answers: 9. (e); 10. (a); 11. (a)

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.

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Helping HF patients feel better with iron

Source: Anker SD, et al. *N Engl J Med* 2009;361:2436-2448.

GLOBALLY DEFINED, HEART FAILURE exists when delivery of oxygen to the tissues is insufficient to meet demand. Anything that compromises oxygen delivery or impairs blood oxygenation can only compound the situation. Accordingly, patients with chronic heart failure (CHF) who are anemic might understandably suffer greater symptom burden or limitations as a result.

Anker et al enrolled patients with CHF (n = 459) and iron deficiency as documented by a low ferritin level. Patients were randomized to receive either placebo or iron intravenously (as ferric carboxymaltose) and followed for 6 months. The primary outcomes of the trial were self-reported global assessment and NYHA functional class.

Iron was administered as a 4 mL bolus IV (200 mg iron) weekly until iron levels were restored (as measured by ferritin, hemoglobin, and transferrin saturation), and then monthly until the end of the trial.

At the end of the trial, both the global assessment and NYHA class were improved to a statistically significant degree more in the iron group than by placebo. There were no serious adverse reactions with the ferric carboxymaltose.

Previous smaller studies have generally had similarly favorable outcomes. Interestingly, both this trial and earlier trials have found that iron supplementation benefits CHF patients with or without anemia, suggesting that more study of the pathophysiologic role of iron in CHF is needed. ■

COPD and osteoporosis

Source: Ferguson GT, et al. *Chest* 2009;136:1456-1465.

OF THE TOP 10 CAUSES OF DEATH IN America, COPD (fourth) might be likened to the Rodney Dangerfield of mortal maladies: "It don't get no respect." Our pulmonology colleagues like to remind us that in contrast to the other 9 top 10 mortal disorders — which are either improving or at least leveling off — COPD mortality is actually rising. One way to awaken clinicians' interest in COPD is to remind them that it's not just about the lungs: Patients with COPD suffer detriment in multiple tissue compartments, such as bone health.

The TORCH trial (Towards a Revolution in COPD Health) studied inhaled fluticasone, inhaled salmeterol, both, or placebo in more than 6000 subjects. A subgroup study (n = 658) looked at the effects on BMD in each treatment arm.

At baseline, more than half of both men and women with COPD had either osteoporosis or osteopenia. Although frank osteoporosis was more common in women (30% vs 18%), osteopenia was equal. This is a critically important observation, since most fractures happen in subjects with osteopenia not osteoporosis. (This is likened to the situation in hypertension: Even though the risk of severe HTN is greater, since there are so many more folks with stage 1 or stage 2 hypertension, most of the CV burden of HTN is not shouldered by folks with severe HTN).

The good news: There was no meaningful change in BMD related to inhaled steroids (alone or in combination with salmeterol). The bad news: Osteopenia and osteoporosis are frighteningly commonplace in COPD. ■

Secondary prevention of depression: Cognitive therapy

Source: Bockting CL, et al. *J Clin Psychiatry* 2009;70:1621-1628.

FOR MILD-TO-MODERATE DEPRESSION, the literature indicates that cognitive therapy (COG) and pharmacotherapy have similar beneficial effects, although pharmacotherapy is often less expensive and may provide symptomatic improvement more quickly. Because depression is recurrent, it is important to identify whether long-term cognitive therapy is helpful to prevent such recurrences.

To investigate this issue, Bockting et al enrolled major depressive disorder patients who had achieved remission (n = 172) and compared usual care with usual care plus COG. The COG was administered as weekly 2-hour group sessions over a 2-month period. After this 2-month COG intervention, both groups were followed for 5.5 years.

The group that had received 8 weeks of COG had a 21% relative risk reduction for recurrence over the next 5 years. Suicide (60% of cases are related to depression) remains in the top 10 causes of death. The value of COG treatment for even as brief a period as 8 weeks

might have substantial long-term clinical payoff. ■

Prediabetes treatment: A wealth of opportunity

Source: Rhee MK, et al. *Diabetes Care* 2010;33:49-54.

It is estimated that almost 40 million Americans have diabetes, and more than twice that many have prediabetes. Clinical trials from the United States and various other nations indicate that prediabetes progresses at a rate of 6%-10% each year to frank diabetes. Fortunately, the menu of interventions that forestall development of diabetes from prediabetes continues to expand. It now includes diet, exercise, metformin, thiazolidinediones, acarbose, and orlistat.

In the recent past, it has been suggested that persons with prediabetes merit pharmacotherapy with metformin (in addition to lifestyle) if they have both impaired fasting glucose and impaired glucose tolerance, and any one of: age > 60 years, BMI > 30 kg/m^2, family history of diabetes, elevated triglycerides, reduced HDL, hypertension, or A1c > 6%.

Rhee et al invited employees of the Grady Health System, Emory HealthCare and University, and Morehouse School of Medicine to be screened for diabetes. Of the volunteers who qualified for glucose tolerance testing (n = 1581), the combination of factors sufficient to merit metformin treatment was 8.1%; an additional 4.6% of subjects were newly diagnosed as frankly diabetic. Now that firm indications for pharmacotherapy of prediabetes are established, clinicians have a wealth of opportunity for timely intervention. ■

Aspirin for primary prevention in diabetes? Maybe

Source: Calvin AD, et al. *Diabetes Care* 2009;32:2300-2306.

The syllogism seemed so simple: 1) The CV risk reduction of aspirin (ASA) in primary prevention is linearly related to baseline risk; 2) DM is a high-risk population for CV events; and 3) therefore, ASA should be really good for primary prevention in diabetics. Well, it's not quite so simple.

The authors of this report in *Diabetes Care* performed a random-effects meta-analysis and Bayesian logistic regression (whatever that means, you ask?) to provide an opinion about whether aspirin is beneficial for primary prevention in diabetes. Their conclusion, based upon 8 trials that included patients with diabetic subgroups among the overall cohort (5 trials) as well diabetes-only trials (3 trials), is that the benefits of aspirin are similar in persons with or without diabetes.

I don't really know what "a random-effects meta-analysis and Bayesian logistic regression" means, but it would appear encouraging that this analysis, which incorporates data from 8 major clinical trials totaling more than 90,000 study subjects suggests, that aspirin might be a good thing.

Trouble is, I'm just not so sure. First, it is a matter of debate whether there is really any such thing as primary prevention in diabetes; after all, adult type 2 diabetics are considered a CV risk equivalent, since their CV risk (without ever having an MI) is as great as a person who has already had one. So, is aspirin in a diabetic primary or secondary prevention?

Secondly, the only 2 recent trials that studied only diabetics and were primarily designed to study the effects of aspirin in diabetics (the JPAD and POPADAD trials) both failed to find a beneficial effect of aspirin.

For the time being, popular opinion suggests that aspirin is a good thing. I'm not so sure. ■

Dementia: No simple answer

Source: Snitz be, et al. *JAMA* 2009;302: 2663-2670.

The burgeoning population of advanced seniors (age > 75 years) includes an ever-growing population of persons with cognitive impairment and dementia. Popular complementary and alternative interventions to forestall dementia abound, among which it has been suggested that ginkgo has memory-preserving qualities.

Unfortunately, the data supporting long-term favorable outcomes for cognitive function are lacking. Nonetheless, because *Ginkgo biloba* has a popular impression of being favorable for mental faculties, and because earlier trials have faced limitations of trial duration, size, and population age, more conclusive insights have been sought.

A study sample of community-dwelling seniors (n = 3069; mean age, 79 years) was administered either 120 mg of ginkgo or placebo twice daily for a median follow-up of 6.1 years. Rates of decline in cognitive function, and numerous other metrics including attention, language, executive function, and others, were not statistically improved by administration of ginkgo. Although there were no significant adverse effects attributable to ginkgo, there is no sound basis on which to advocate for long-term cognitive effects from ginkgo. ■

Correction

In the January brief entitled "The relationship of FPG and A1c to diabetic retinopathy" (page 1), the recommended A1c threshold for the diagnosis of diabetes should have read 6.5% instead of 6.2%. ■

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Oral Treatments for Relapsing-remitting MS

In this issue: Two oral medications for relapsing-remitting MS in phase III development; antihypertensives find new uses; *Ginkgo biloba* does not prevent cognitive decline in elderly; and FDA Actions.

Oral medications for relapsing-remitting MS

Two new oral medications are effective treatments for relapsing-remitting multiple sclerosis (MS) according to three studies published on-line in the *New England Journal of Medicine*. Fingolimod and cladribine differ in the mechanism of action but both reduce the number of potentially auto-aggressive lymphocytes that are available to enter the central nervous system. In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) trial, two different doses of cladribine were compared to placebo with the endpoint being relapse at 96 weeks. Both doses were more effective than placebo at preventing relapses and reducing brain lesion count on MRI ($P < 0.001$ for all comparisons). The drug was associated with lymphocytopenia and a higher risk of herpes zoster.

Fingolimod was compared to placebo in the FREEDOMS trial and compared to injectable interferon in the TRANSFORMS trial. The 24-month FREEDOMS trial compared two doses of fingolimod to placebo and similarly found a lower rate of relapse ($P < 0.001$ for both doses) and disability progression ($P = 0.02$ for both doses). The drug also reduced the number of new lesions found on MRI. Significant side effects included bradycardia, AV block, macular edema, elevated LFTs, and mild hypertension. When compared to interferon, fingolimod was associated with significantly lower annualized relapse rates at both doses tested ($P < 0.001$ for both comparisons), although there was no significant difference with respect to progression of disability. Two fatal infections occurred with the higher dose of fingolimod (disseminated primary varicella zoster and herpes simplex encephalitis). (All three studies published on-line at www.NEJM.org, Jan. 20, 2010).

An accompanying editorial calls the arrival of oral formulations of MS drugs "welcome news for the estimated 2.5 million people worldwide with this chronic, disabling disease." While suggesting these drugs "support a change in treatment approach to directly prevent immune-related injury," the editorial also suggests that long-term goals of MS therapy are currently lacking (published online at www.NEJM.org, Jan. 20, 2010). Both drugs are in phase III trials for treatment of MS; cladribine is currently approved in parenteral form for treatment of hairy cell leukemia. ■

Antihypertension drugs for AF and dementia?

Different classes of blood pressure (BP) medications may have different benefits according to two new studies. In the first study, researchers from the United Kingdom performed a nested

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case-control analysis to evaluate whether different antihypertensive drug classes may alter the risk for atrial fibrillation. The researchers reviewed records from a large patient population, specifically patients who were on a single agent for lowering BP. A lower odds ratio (OR) for atrial fibrillation was noted with ACE inhibitors (OR, 0.75; 95% confidence interval [CI], 0.65-0.87), angiotensin receptor blockers (ARBs) (OR, 0.71; 95% CI, 0.57-0.89), and beta-blockers (OR, 0.78; 95% CI, 0.67-0.92) compared with current exclusive therapy with calcium channel blockers. Although the researchers were unable to assess why patients were receiving one class of blood pressure medicine over another, they concluded that long-term therapy with ACE inhibitors, ARBs, or beta-blockers reduces the risk for atrial fibrillation compared with calcium channel blockers. These findings generally relate to patients with mild hypertension, since patients on multiple drugs were excluded from the study (*Ann Intern Med* 2010;152:78-84).

In the second study, researchers from Boston set out to investigate whether ARBs reduce the risk of Alzheimer's disease and dementia or reduce the progression of both diseases. More than 800,000 predominately male participants, age 65 or older with cardiovascular disease, were studied. Patients were divided into three cohorts (ARBs, lisinopril, and other cardiovascular drugs as a comparator) and followed over 4 years, with adjustments for age, diabetes, stroke, and cardiovascular disease. Hazard rates for dementia in the ARB group were 0.76 (95% CI, 0.69-0.84) compared to the cardiovascular comparator, and 0.81 (95% CI, 0.73-0.90) compared to the lisinopril group. In patients with pre-existing Alzheimer's disease, ARBs were associated with significantly lower risk of admission to a nursing home. The combination of the ARB and ACE inhibitor was better than ACE inhibitor alone in preventing dementia and reducing admission to nursing home. The authors conclude that ARBs are associated with a significant reduction in the incidence and progression of Alzheimer's disease and dementia compared to ACE inhibitors or other cardiovascular drugs (BMJ 2010;340:b5465, doi: 10.1136/bmj.b5465, published on-line Jan. 12, 2010). An accompanying editorial points out that several studies have shown that treatment with any antihypertensive is associated with a lower risk of cognitive decline or incident dementia in older adults. What is not clear is whether some antihypertensives also have other biological mechanisms that help prevent dementia. It is plausible that ARBs are more neuroprotective than other drugs because of their effect on type 2 angiotensin receptors in the brain (*BMJ* 2010:340;b5409, doi: 10.1136/bmj.b5409, published on-line Jan. 12, 2010). ■

Ginkgo does not prevent cognitive decline

The National Center for Complementary and Alternative Medicine (NCCAM) was founded during the Clinton administration as part of the National Institutes of Health to investigate complementary and alternative medicines. Many of the NCCAM-funded studies, however, have shown no benefit from complementary or alternative treatments, and that is the case with a new study looking at *Ginkgo biloba* and cognitive function in older adults. *Ginkgo biloba*, which is widely marketed as an aid to preventing cognitive decline and dementia, was previously found to have no benefit in reducing the incidence of Alzheimer's disease or dementia overall (*JAMA* 2008;300:2253-2262).

In a new study sponsored by NCCAM, researchers set out to determine whether *Ginkgo biloba* slows the rate of global or domain-specific cognitive decline in older adults. More than 3000 participants age 72-96 years were enrolled and randomized to *G. biloba* 120 mg or placebo twice daily. Rates of change over time in two different objectives cognitive tests, as well as neuropsychological tests, were the primary endpoints. There was no difference in the decline in cognitive scores between *Ginkgo biloba* and placebo in any of the domains including memory, attention, and visuospatial abilities, language, or executive functions. There was also no difference in the rate of change in the standardized cognitive exams. The authors conclude that compared to placebo, *Ginkgo biloba* did not result in less cognitive decline in older adults (*JAMA* 2009;302: 2663-2670). ■

FDA Actions

Novo Nordisk has received approval to market liraglutide, a once-daily injection for the treatment of type 2 diabetes in adults. The drug is a glucagon-like peptide-1 receptor agonist similar to exanatide (Byetta®). The company is required to perform additional post-marketing cardiovascular studies as well as a 5-year epidemiological study to evaluate the risk of thyroid cancer. Liraglutide will be marketed under the trade name Victoza®. ■