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Clinical Oncology
A monthly update of developments in cancer treatment and research [ALERT]

ILLUSTRATIVE CASE SERIES

CLL and Hemolytic Anemia

By Charles Hesdorffer, MD
National Institute of Health
Dr. Hesdorffer reports no financial relationship relevant to this field of study.

A 67-YEAR-OLD PREVIOUSLY HEALTHY MAN WAS REferred from his primary care physician because of an abnormal CBC. Although he had noted gradually increasing fatigue over approximately six months, this had become noticeably worse and, for this reason, he went to the doctor. He had not experienced night sweats or weight loss and had no localizing symptoms.

Upon physical exam, there was notable pallor. He was afebrile, his blood pressure was 118/76, and his pulse was 100. There was no palpable lymphadenopathy, but the spleen was palpable 4 cm below the left costal margin. The remainder of his physical examination was normal.

Complete blood count revealed a WBC of 44,000/cu mm, with a differential of 14% neutrophils, 4% bands, 2% monocytes, and 80% small lymphocytes with "smudge" cells noted. Hemoglobin was 6.5 g/dL, hematocrit was 20%, and MCV was 88.

DIAGNOSTIC CONSIDERATIONS

There is very little doubt that this individual has a leukemic process, most likely chronic lymphocytic leukemia or CLL. This degree of lymphocytosis, the characteristic lymphocyte predominance with such a high absolute lymphocyte count, and the presence of smudge cells are all typical features, and are diagnostic of little else. At this juncture, the questions are: What type of CLL does he have, does he have clinical issues that arise from his CLL that require therapeutic intervention, and what is his prognosis?

REQUIRED VS. OPTIONAL DIAGNOSTIC CONFIRMATION AND TESTING

A bone-marrow test may be helpful but frequently is

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not necessary to establish the diagnosis of CLL. One can confirm the diagnosis with peripheral blood flow cytometry. Marrow analysis may be useful in certain situations. For example, a patient who is treated for active, symptomatic disease and appears to have responded clinically but without improvement counts. Here the question is whether the patient's disease is refractory or the marrow has become hypoplastic due to the treatment.

I would, thus, start with laboratory studies to define the nature and extent of the disease. Flow cytometry would confirm the presence of a B- or T-cell CLL vs. any other similar chronic lymphoid malignancy, such as LGL leukemia or Hairy Cell Leukemia, with the typical finding of a B-cell phenotype, usually lambda or kappa light-chain restricted, confirming clonality and expressing CD20 (usually dim), CD23 and, in most patients, CD5 and CD52, with CD10 being negative.

Additional blood studies should include: a chemistry profile (for renal and hepatic function), B2-microglobulin, LDH, ESR, CRP, iron panel, ferritin, reticulocyte count, red cell folate level, haptoglobin, Coombs test, immunoglobulin panel, and IPEP, as hypogammaglobulinemia is both common in untreated and especially in patients treated with CD20 antibody (rituxan and ofatumumab). Many patients also may have a monoclonal serum spike that should be followed carefully through the course of their disease (especially in the setting of patients who have an IgM spike and who may thus have a Waldenstrom's macroglobulinemia).

A CT scan of neck, chest, abdomen, and pelvis should be obtained and followed as clinically indicated. Finally, although CNS involvement with CLL is extremely uncommon, if patients present with neurological signs, the initial workup should include brain CT, MRI, and lumbar punctures.

The current case highlights one of the nuances of CLL in that the disease is occasionally associated with autoimmune features, such as ITP or hemolytic anemia. Under such circumstances, the diagnostic strategy could include a bone marrow aspirate to confirm the presence of adequate or increased red cell and platelet precursors. For anemic patients, a Coombs and reticulocyte count are useful to discriminate between hemolysis and decreased marrow production.

TREATMENT CONSIDERATIONS

CLL is characterized by a highly variable clinical course. Some patients are symptomatic at diagnosis, or early thereafter, and require early therapy. Others have no or minimal symptoms for many years, and may have a normal life expectancy. Treatment of early-stage and low-risk patients has not been shown to prolong survival. Nonetheless, recently introduced, highly effective, and potentially curative interventions have resulted in a need to reassess this position. Therapies, including monoclonal antibodies directed against specific cell surface markers, used alone or in combination with other antibodies or chemotherapy, and autologous or allogeneic stem-cell transplantation hold the promise of more effectively reducing tumor burden to the point where prolonged survival and even disease eradication (allogeneic transplantation only) in selected patients would be expected. Our improved understanding of the molecular pathophysiology of CLL, and of the underlying immune deficiency, have made decisions regarding treatment both more rational but also more complicated because of the conflicting features of the disease in many patients.

The progress in understanding the pathogenesis, as well as in predicting outcomes, has led to the development of curtailed and potentially less toxic treatments. A number of clinical and biological markers of prognostic relevance have been identified. These include clinical characteristics (e.g., age, stage, gender, and performance status), as well as laboratory parameters (e.g., lymphocyte count, lactate dehydrogenase [LDH], marrow infiltration pattern, lymphocyte doubling time, soluble CD23 [sCD23], beta 2-microglobulin [B2-MG], or thymidine kinase [TK]). More recently, prognostic markers related to the biology of CLL have been identified.

DEFINED TREATMENTS AND STRATEGIES

High-risk Patients: In the setting of any patient with a 17p deletion, since the prognosis is the worst for these patients based on almost all studies reviewed, no matter how many other

mitigating prognostic factors these patients may have, this group, in general, can be dealt with by advising the patient to enter a clinical trial. Alternatively, bone-marrow transplantation is an acceptable modality of treatment for this select group of patients. However, the benefit of this modality of therapy is restricted by age (generally < age 60, which is in and of itself an issue of great controversy) and the general performance status of the patient. Furthermore, its use is also clearly dependent upon the accessibility of a matched-related or unrelated donor, although giant strides are possible in the near future in terms of the use of cord blood or haploid identical donors.

An antibody that interacts with the CD56 surface antigen on B and T cells, alemtuzumab has been demonstrated to improve the survival of these patients. However, this agent causes significant and prolonged immune deficiency, and prophylactic use of antimicrobial antibiotics is recommended.

Most other treatment strategies generally used in CLL, such as rituxan, fludarabine and, thus far, bendamustine, have proven to be relatively inactive in changing the natural history of patients with this poor prognostic marker.

Low-risk Patients: Patients who demonstrate a full set of good prognostic features (low burden of disease, normal B2-microglobulin, the absence of any clinical features indicating complications from CLL, 13q deletion, mutated Ig H chain, and absent CD38 surface marker) should receive no treatment and be watched until such time as either they demonstrate complications from their disease or some form of transformation to a higher grade of disease is noted.

Additionally, treatment for autoimmune complications are important as the sudden development of anemia and thrombocytopenia can be debilitating and if immune mediated can readily reversed. Thus, in the case presented here, I would elect to treat with single-agent rituximab (anti-CD20) and follow carefully to assess whether such treatment reverses what I believe to be a CLL-associated autoimmune hemolytic anemia.

In summary, most patients will be treated with their risk stratification being a thoughtful compilation of all risk factors by the treating physician. Hopefully, in the next few years, longitudinal and epidemiological studies will allow even more precise risk stratification, and our ever-increasing understanding of the molecular and genetic alterations that characterize this disorder will result in selected therapies that will more effectively alter the natural history of this disorder. ■

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RAPID REVIEW

Surgical Resection of Colon Cancer Liver Metastases

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

Approximately half of colon cancer patients will develop liver metastases during the course of their disease, but only about 20% of patients with hepatic metastases are candidates for surgical resection. Criteria for resectability include no radiologic evidence of involvement of the hepatic artery, portal vein, or major bile ducts, no local lymph node involvement, and adequate reserve in the remaining liver. An analysis of 3,957 Medicare patients who had surgical resection of liver metastases from 2000-2004 demonstrated a 25% five-year survival, with 30- and 90-day mortality rates of 4% and 8%, respectively. Indicators for poor short- and long-term mortality were age > 80, comorbid disease, and synchronous colon/hepatic resection.[1] Given that the five-year survival for patients with metastatic colorectal cancer after chemotherapy is only 10%, surgical removal of liver metastases should be attempted if there is a reasonable chance for complete resection.

With more active chemotherapy regimens and better surgery, patients with multiple, bilobar metastases can be candidates for resection, with five- and 10-year survivals in the 50% and 30% range, at least in a small series of highly selected patients.[2] It is generally recommended that when four or more lesions are present, neoadjuvant

chemotherapy should be used to determine the responsiveness and biologic behavior of the patient's cancer, and to improve chances of obtaining clear margins at surgery. Post-operative chemotherapy is imperative to reduce the high recurrence rates after surgery, especially in cases with large numbers of metastases (e.g., > 7). A randomized study comparing resection of hepatic metastases, with or without perioperative FOLFOX4, demonstrated a significant increase in progression-free survival of 7%-9% in the chemotherapy group.[3] At 3.9 years of follow-up, there was a three-year DFS trend favoring the chemotherapy arm (35 vs. 28%, $p = 0.058$).[3] The role of hepatic artery infusion (HAI) after the resection of hepatic metastases is being studied in NSABP C-09, which is comparing systemic capecitabine plus oxaliplatin alone or combined in alternating cycles with HIA infusion of FUDR.

For patients with four or fewer lesions that appear resectable, it is reasonable to either administer neoadjuvant chemotherapy or to perform surgery and then give adjuvant chemotherapy. Neoadjuvant chemotherapy with oxaliplatin or irinotecan-based regimens can cause liver toxicity (sinusoidal dilatation or steatohepatitis, respectively) that may increase the post-operative complication rate.[4,5] Therefore, for healthy patients with four or fewer metastases, surgery should be performed first, followed by adjuvant chemotherapy. For patients with borderline or initially unresectable disease, neoadjuvant chemotherapy should be given to determine responsiveness and to render the patient operable if they respond. Using FOLFOX, FOLFIRI, or a hybrid, as many as 30%-40% of "unresectable" patients can be converted to the "potentially curable with surgery" category. In all cases, bevacizumab, or EGFR-targeting antibodies (cetuximab, panitumumab), should be combined with chemotherapy regimens to enhance the anti-tumor response, realizing that a 6-8 week interval between bevacizumab and surgery is recommended. Additionally, surgery should be delayed until four weeks after the last chemotherapy treatment to allow liver toxicities to abate.

When neoadjuvant chemotherapy with newer, active agents is used, it is not uncommon for some of the liver metastases to completely respond, as determined by CT imaging. The surgeon must then ponder the question as to how to deal with liver lesions that are no longer visible on preoperative-staging CT scans. Should these liver segments be excised, thereby expanding the operation and increasing morbidity, or can they be assumed to be free of disease, as suggested radiologically? Data from a study designed to directly answer this question will be reviewed, and their implications for the concept of colon cancer stem cells will be discussed.

Benoist et al prospectively studied 586 consecutive patients from 1998 to 2004, of which 38 patients met the inclusion criteria;[6] fewer than 10 had liver metastases prior to chemotherapy; imaging showed the disappearance of at least one metastasis after chemotherapy; surgery with intra-operative ultrasound within four weeks of CT scanning; no extra-hepatic disease; no previous liver resection or radiofrequency ablation; and at least one year of follow-up after surgery. In the 38 eligible patients, 183 liver metastases were identified prior to the chemotherapy, of which 66 had completely responded on preoperative imaging. The average maximum diameter of these lesions was 2.2 ± 1.5 cm; no lesions greater than 4.5 cm completely responded. The goal of the study was to determine how many of these 66 lesions were really sterile.

During surgery, direct liver inspection and ultrasound found residual macroscopic disease in 20 of these sites (24%), which had a mean size of 12.1 ± 6.8 mm (range 3 to 25 mm). Eight of the nine patients with macroscopic residual disease had been considered unresectable prior to chemotherapy; of these, six were rendered NED and two could not be completely resected. Forty-six patients had no macroscopic residual tumor at sites of pre-treatment lesions. These lesions were treated in one of two ways: The site of the initial resection was resected (15 cases), or the site of initial metastasis was not removed and followed over the ensuing year of the study by CT imaging (31 patients). In the former group, viable tumor cells were detected in 12 of the 15 patients (80%), and only three were free of viable tumor; ten of the 15 patients recurred within one year of surgery. In the latter group, recurrence at the original site of metastasis occurred in 23 of the 31 patients (74%), and only eight remained free from recurrence at the initial site. Overall, in 55 of 66 (83%) of the liver metastases that had shown a CR on preoperative CT scans, residual microscopic or macroscopic disease, or early recurring disease, was identified.

Clearly, complete response by CT imaging does not equate to sterilization of the site for colorectal cancer hepatic metastases, and these liver segments must be included in the surgical resection plan. However, there are a few caveats to the data. It is not clear the patients in this study received optimal chemotherapy, since some patients received only six courses and others received 5-FU/LV without oxaliplatin or irinotecan. Furthermore, it is possible that the addition of bevacizumab or cetuximab would have significantly improved the data, although neither of these agents, when added to first-line chemotherapy, has been shown to be active against minimal residual disease. Furthermore, it is possible that the surviving tumor cells represented in minimal residual disease are not representative of the metastatic site as a whole. Dick et al have demonstrated the existence of colon cancer stem cells using murine xenograft transplantation studies in a manner analogous to experiments that led to identification

of leukemia stem cells.[7] Hence, one can postulate that viable cells remaining at metastatic sites after neoadjuvant chemotherapy are colon cancer stem cells, or cells with characteristics of stem cells, which render them resistant to current forms of chemotherapy. This hypothesis will be difficult to prove, since isolating and characterizing these cells from surgically resected tissue will be challenging, although, perhaps, not impossible. Understanding what these remaining viable tumor cells are, and characterizing the signaling pathways responsible for their survival, will be critical for the development of targeted therapies that can truly sterilize sites of colorectal cancer metastases. ■

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ABSTRACT & COMMENTARY

CEA FLARE AND COLORECTAL CANCER: A GOOD PROGNOSTIC SIGN

By William B. Ershler, MD

Synopsis: *Within a large series of colorectal cancer patients receiving initial chemotherapy, a prompt rise and then drop in CEA level (flare) was observed in 11.6%. Compared with patients who had a continuous rise in CEA, those exhibiting a flare reaction had improved response to chemotherapy and progression-free and overall survival.*

Source: Strimpakos AS, et al. The impact of carcinoembryonic antigen flare in patients with advanced colorectal cancer receiving first-line chemotherapy. *Ann Oncol.* 2010;21:1013-1019.

THERE IS EVIDENCE FROM PREVIOUSLY PUBLISHED SMALL series of patients with advanced colorectal cancer that carcinoembryonic antigen (CEA) flare (a prompt rise in CEA titer after initial chemotherapy) may be an indication of favorable response to chemotherapy,[1,2] but whether this translates to improved survival remains unknown. Strimpakos et al from the Royal Marsden Hospital (London) performed a retrospective review of 670 eligible patients with advanced colorectal cancer who received initial chemotherapy at their institution between January 2000 and February 2008. The study aimed to evaluate the incidence of CEA flare and its impact on objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). For the study, a CEA flare was defined as a ≥ 15% rise from baseline (at least 4 ug/L), followed by a subsequent ≥ 15% decrease from baseline in CEA level within four to six weeks of initial treatment.

Patients with histologically proven advanced colorectal cancer undergoing first-line chemotherapy with three or more serial CEA measurements (one at baseline and two or more during treatment) were included. By analysis of serial CEA measurements, patients were considered in one of five categorical groups: 1) CEA flare; 2) decreasing CEA; 3) normal baseline CEA; 4) stable CEA; or, 5) increasing CEA.

Seventy-eight of 670 (11.6%) patients demonstrated the CEA flare phenomenon. The median baseline CEA value in the flare group was 74 ug/L (range 5–31 480 ug/L), and the median peak CEA value was 115 ug/L, reached in 21 days (range 4–61 days). The median duration of CEA flare (from date of baseline CEA to date of first CEA level below the baseline) was 49 days (range 16–117 days).

On multivariate analysis, compared with patients with increasing CEA (group 5), patients with CEA flare had

a significantly better ORR (group 5 vs. group 1: 11% vs. 73%; risk ratio [RR]: 27.96; 95% CI: 9.55–81.88; $p < 0.001$), PFS (median 3.1 vs. 8.3 months; RR: 0.38; 95% CI: 0.26–0.56; $p < 0.001$) and OS (median 10.9 vs. 17.7 months; RR: 0.53; 95% CI: 0.34–0.82; $p < 0.001$).

In addition to the flare, this study also showed that a decreasing CEA pattern (group 2) and a normal baseline (group 3) were also associated with improved PFS and OS when compared to the increasing pattern (group 5). The number of patients in the "stable" CEA group (group 4) was insufficient to demonstrate a survival benefit.

■ COMMENTARY

Thus, CEA flare was associated with a 62% relative reduction in the risk of progression and a nearly halving of the risk of death compared to an increasing CEA pattern. It is notable that patients with normal baseline CEA levels exhibited the best progression-free and overall survival. Nonetheless, this comprehensive analysis of a large series of colorectal cancer patients confirms and extends the favorable implications of CEA flare. In the previous reports, flare was associated with an improved response rate; in this report of a substantially larger series, not only was improved response rate observed, but also there was improved progression-free and overall survival compared with those whose with rising CEA levels in a pattern other than "flare."

Why this should be the case remains unknown. CEA is a glycoprotein normally found in embryonic tissue and various adenocarcinomas but not in healthy normal adult tissue.[3] It remains unclear whether its presence has any significance with regard to local tumor growth, invasion, and metastases, or whether its level just signifies the overall burden of tumor cells. There are some experimental tumor models that would support the first hypothesis. For example, injection of exogenous CEA in a murine colorectal cancer model resulted in increased liver metastases.[4] A mechanism accounting for a "flare" in CEA in a subset of treated patients also remains to be established. There is a current sense that CEA flares may be more prevalent in patients treated with oxaliplatin[2,5] and, if so, we might expect to see more patients exhibiting a flare as more patients with advanced colorectal cancer are treated with this drug. ■

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ABSTRACT & COMMENTARY

INVASIVE ASPERGILLOSIS AND AML

By Andrew S. Artz

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Dr. Artz reports no financial relationship relevant to this field of study.

Synopsis: *Invasive aspergillosis remains a problematic complication of therapy. The authors prospectively evaluated IA infections among AML patients at 21 centers. Among 140 cases of probable or definite IA, attributable mortality was 27%. Relapsed/refractory AML and lack of recovery from neutropenia were the strongest adverse prognostic factors. Most patients underwent empirical or pre-emptive therapy. Response rate varied by agent from amphotericin, caspofungin, and voriconazole but was not statistically different. Invasive aspergillosis-related mortality for AML patients continues to improve although mortality remains substantial.*

Source: Pagano L, M. et al. Invasive Aspergillosis in patients with acute myeloid leukemia: A SEIFEM-2008 registry study. *Haematologica.* 2010;95:644-650.

Invasive fungal infections have been a long-feared complication in treating patients with hematologic malignancies. Aspergillosis is the most common invasive fungal infection, as many have adopted routine anti-yeast prophylaxis for *Candida albicans*. A recent series confirmed for AML patients, aspergillosis persisted as the most common invasive fungal infection.[1] Neutropenia and immune suppression are the principal risk factors for invasive aspergillosis (IA).[2] The epidemiology of IA may be changing with the availability of better diagnostic tools and additional aspergillosis agents. Some data do suggest improving outcomes over time related to IA infections.[1]

The authors embarked on a prospective registry study to characterize the epidemiology and outcomes related to IA among AML patients; twenty-one Italian centers participated. Prior hematopoietic cell transplantation was excluded, or patients who had already received two or more chemotherapy regimens. Between 2004 and 2007, 140 cases of proven or probable IA were identified. The median age was 57 years, and 85 (60%) occurred during aplasia from initial induction therapy. The lung represented the most common site of infection (90%), and almost all cases occurred in the setting of severe neutropenia (93%). On average, 12 days elapsed between symptom onset and diagnosis of IA. *Aspergillosis fumigatus* was the most common subspecies. The majority of patients (86%) generally received antifungal prophylaxis using itraconazole or fluconazole. Therapy was empiric in 62% and pre-emptive in 29%. G-CSF was initiated in two-thirds of patients as part of the treatment plan.

Mortality by day 120 was 33%. Death was related to IA in 38/140 (27%). As expected, patients having relapsed/refractory AML harboring an IA infection fared much worse than those in remission (43% compared to 19%, $p = 0.002$). Prolonged neutropenia of 10 days or more was associated with increased IA-attributable mortality. G-CSF administration was associated with reduced neutropenia, but did not alter IA-related mortality. No anti-mold drug was linked to better outcomes, with the three most common drugs being amphotericin preparations, caspofungin, and voriconazole. A good response to therapy for IA occurred in 71%.

■ COMMENTARY

Invasive fungal infections remain one of the most feared complications from immunosuppressive and highly myelosuppressive therapy. Of these, IA is the most common.

The findings of these studies mirror other published studies. Most infections were identified in the lung during neutropenia. Prolonged secondary G-CSF therapy (i.e., started for signs or symptoms of infection) was associated with faster neutrophil recovery than non-G-CSF therapy, but did not improve outcomes related to IA. Granulocytic transfusions were only given to two patients, so could not be assessed. The response rates to first-line therapy in 101 evaluable patients were 68%, 61%, and 84%, respectively, for liposomal amphotericin, caspofungin, and voriconazole. This was not statistically different, and baseline characteristics were not necessarily similar. Around 16% of patients received two aspergillosis-active drugs, usually added sequentially.

Overall, aspergillosis-attributable mortality was 27%, indicating continued improvements in outcomes over time. As expected, patients having relapsed/refractory AML harboring an IA infection fared much worse than those in remission (43% compared to 19%, $p = 0.002$). Prolonged neutropenia of 10 days or more was associated with increased IA-attributable mortality.

To put the results in context, patients only received prophylaxis with fluconazole or itraconazole. Fluconazole is inactive against aspergillosis, and itraconazole has limited activity. Whether aspergillosis-active drugs such as voriconazole and posaconazole should be used for prophylaxis remains an area of controversy. Routine prophylaxis would add significant cost and possibly toxicity. The strategy of empiric therapy (started with signs or symptoms of infection) or pre-emptive therapy (signs and symptoms and suspicion for aspergillosis) appears to have had a high success rate. Specifically, response rate overall to single therapy was 71%, and as high as 84% for voriconazole. Interestingly, most patients received empirical or pre-emptive therapy, suggesting better diagnosis, awareness, and/or low threshold to employ IA treatment. IA-related mortality was 27%, indicating marked improvement from historic results.

Voriconazole has improved activity compared to conventional (non-lipid) amphotericin.[3] The response rate in a large randomized trial for voriconazole was 53%, but many patients had undergone hematopoietic stem-cell transplantation, a higher-risk group of patients.

The improvement in historically dismal outcomes certainly stems, in part, from more tolerable, if not more effective, drugs, such as echinocandins and extended spectrum azoles (e.g., voriconazole). Still, other advances, such as improved detection through high-resolution CT scanning, rapid bronchoscopy, and/or galatomman assay, may also play important roles.

In summary, aspergillosis remains a problematic infection for AML patients. Although mortality is sig-

nificant, response rates and attributable mortality continues to improve, probably related to more active anti-aspergillosis therapy. For physicians treating AML, one must have a high index of suspicion for IA and consider early pre-emptive or empirical therapy. ■

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CME Questions

18. What prognostic factors were identified to adversely impact outcomes for invasive aspergillosis among AML patients?

a. Presence of relapsed or refractory AML.
b. Shorter period of neutropenia.
c. Use of G-CSF for secondary prophyalxis.
d. Pulmonary involvement

19. In patients with advanced colorectal cancer, observation of a prompt rise in CEA level after initial therapy and then a drop below baseline level (flare) compared with a continuously rising pattern of CEA levels, is associated with which of the following outcomes:

a. Improved response rate
b. Improved progression free survival
c. Improved overall survival
d. All of the above
e. None of the above

20. For healthy-performing patients with colon cancer and 4 or fewer liver metastases apparent on imaging studies, which of the following approaches is currently most favored:

a. Chemotherapy followed by repeat imaging studies. If CR is apparent, no surgical resection.
b. Neoadjuvant chemotherapy followed directly by surgery.
c. Surgical excision.
d. Surgical excision followed by adjuvant chemotherapy.

Answers: 18. (a); 19. (d); 20. (d)

CME Objectives

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

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
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7. I detected no commercial bias in this activity.	○	○	○	○	○	○
8. This activity reaffirmed my clinical practice.	○	○	○	○	○	○
9. This activity has changed my clinical practice.	○	○	○	○	○	○

If so, how? _____

10. How many minutes do you estimate it took you to complete this entire semester (6 issues) activity? Please include time for reading, reviewing, answering the questions, and comparing your answers to the correct ones listed. _____ minutes.
11. Do you have any general comments about the effectiveness of this CME program?

_____

I have completed the requirements for this activity.

Name (printed) _____ **Signature** _____

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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Zinc and vitamin C for pressure ulcers?

Source: Jamshed N, Schneider JI. Is the use of supplemental vitamin C and zinc for the prevention and treatment of pressure ulcers evidence-based? *Annals of Long-Term Care: Clinical Care and Aging* 2010;18:28-32.

ELDERLY PATIENTS, PARTICULARLY THOSE residing in nursing homes, are at risk for pressure ulcers (PrU) with recent reviews indicating a nursing home prevalence approximating 10%. Prevention and treatment of PrU commonly includes zinc and vitamin C (Z&C), based upon observations (animal studies) that both are necessary for optimum wound healing. Additional support for this concept comes from recognition of the sometimes marginal nutritional status of senior citizens. Some studies have shown malnutrition to result in an increase risk for PrU by as much as two-fold, but other studies disagree.

For vitamin C, a study performed in the 1970s reported increased wound healing, but the study only contained 20 patients, and subsequent trials have not been able to consistently show similar improvements.

For zinc, one study of senior citizens (n = 672) showed a small but statistically significant difference favoring supplementation, but study design and confounding issues preclude a final word on the subject. Overall, studies have been infrequent, small, and unable to provide a definitive conclusion.

Although generally considered safe, zinc and vitamin C do have associated adverse effect profiles, including increased risk of oxalic acid stones (vitamin C) and copper deficiency (high-dose zinc).

Based upon their literature review, the authors conclude that supplementation of Z&C above recommended dietary intake is not supported, and could have important adverse effects.

Dutasteride reduces prostate cancer risk

Source: Andriole GL, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010;362:1192-1202.

THE PROSTATE CANCER PREVENTION TRIAL did not ignite advocacy among clinicians for chemoprevention of prostate cancer (PCA). Although this large trial showed an overall reduction in total cancers (about 23%), high-grade tumors were actually statistically significantly increased. Several reasonable explanations for this phenomenon were offered; however, the disquieting consideration that 5-alpha-reductase inhibitors might be efficacious for reduction of low-grade tumors — but not effective for the more important high Gleason score tumors — remained.

Dutasteride and finasteride are very similar in their effects on the prostate, although there are both pharmacokinetic and pharmacodynamic differences. For instance, dutasteride has a much longer half-life (5 weeks), and dutasteride blocks both arms of the 5-alpha-reductase pathway (types 1 and 2), whereas finasteride only blocks type 2. Because both agents are highly efficacious in reducing intraprostatic levels of dihydrotestosterone, the putative culprit in generating BPH and possibly related to development of PCA, many experts consider them clinically comparable.

The REDUCE Trial (Reduction by Dutasteride of Prostate Cancer Events) enrolled men age 50-75 with a PSA of 2.5-10 ng/mL with negative prostate biopsy at baseline. Subjects were randomized to dutasteride 0.5 mg/day or placebo and followed for 4 years, receiving biopsies at year 2 and year 4.

At the completion of the trial, dutasteride was associated with an overall PCA relative risk reduction of 23%; encouragingly, this trial did not show a statistically significantly increased risk of high Gleason score tumors. Because dutasteride also provides favorable symptom benefits for BPH, clinicians may want to re-examine the balance of risks and benefits of 5-alpha-reductase inhibitors.

New short-course topical treatment for actinic keratoses

Source: Swanson N, et al. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. *J Am Acad Dermatol* 2010;62: 582-590.

ACTINIC KERATOSES (AKS) RECENTLY HAVE been recognized as both a cosmetic and a dermatopathologic problem, since they are precursors to squamous cell carcinoma. Indeed, current literature suggests that AKs be considered squamous cell carcinoma in situ. AKs treatment includes cryotherapy, excision, chemical destruction (e.g., 5-fluorouracil, diclofenac), immune activation (imiquimod [IMQ]), and others. Because topical treatment courses

are sometimes protracted, and induce unpleasant cutaneous inflammatory changes, clinicians desire simpler, gentler methods.

Swanson et al randomized patients with AKs on the face and scalp to IMQ or placebo (n = 479). IMQ was applied as pulse therapy: qd for 2 weeks, then no treatment for 2 weeks, then repeat (total = 14 days of treatment). Outcomes were measured at 8 weeks.

IMQ produced a 72%-82% reduction in AKs lesions; higher doses produced complete clearing in 59% (vs 6% with placebo). A companion article in the same journal showed similar clearance rates for a longer regimen (3-week treatment courses). This simpler regimen was well tolerated, and provides a quick and effective route for topical treatment of AKs.

After bariatric surgery: The role of exercise

Source: Evans RK. Maintaining weight loss momentum after bariatric surgery. *Am J Lifestyle Med* 2010;4:124-127.

Bariatric surgery is increasingly recognized as a rational therapeutic option for morbid obesity and obese patients with comorbidities such as diabetes. On average, bariatric surgery produces a 35% reduction in body weight, but patients regain varying amounts of weight over time. Studies of the role of diet after bariatric surgery have helped to direct long-term postoperative dietary management, but less information is available to guide exercise advice.

In the period after postoperative weight-loss stabilization, the weekly amount of exercise does correlate with sustained weight loss. Unfortunately, 37%-51% of postoperative subjects have been found to be noncompliant with exercise recommendations. Curiously, adherence to exercise in some trial data was greater before surgery than afterward, as if subjects felt they no longer needed exercise to the same degree now that surgery had been performed.

Bariatric surgery does not completely and permanently resolve weight-management issues in obese subjects. The high frequency with which post-surgical patients are noncompliant with exercise recommendations, with anticipated weight gain consequences, should spur clinicians to bolster patient education.

What aspect of HTN produces toxicity?

Source: Rothwell PM, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010;375:895-905.

A well-established body of epidemiologic literature supports a continuous graded risk between systolic blood pressure (SBP) and CV risk. This relationship has held constant whether one considers office BP, home BP, or ambulatory blood pressure monitoring (ABPM). Because BP is variable over time, it is unclear whether the toxicity of BP to the vasculature is more strongly associated with mean BP, maximum BP, pulse pressure (SBP − DBP), or BP variability. Circadian rhythm of BP has also been recognized to be particularly associated with adverse outcomes: ABPM subjects whose BP does not decline overnight (called non-dippers) have greatly increased CV risk, well beyond what would be expected simply by having a greater total number of hours of exposure to elevated BP.

Rothwell et al used a data set comprised of persons who had sustained a TIA in large clinical trials (n = 2006), including the UK TIA Trial and ASCOT. Visit-to-visit BP variability and maximum SBP were better predictors of adverse outcome than mean SBP. Similarly, persons with episodic HTN (normal BP on some occasions, elevated on others) were also at increased stroke risk, surpassing risk for stable BP.

It remains to be elucidated why these subgroups of individuals with BP variability have a greater risk burden. Although the associations between maximum SBP, BP variability, and episodic BP elevations were consistent, this does not establish causation. Perhaps the strongest cautionary message from this trial is that clinicians should not fall prey to false reassurance when they see a mixed BP response pattern including some BP measurements at goal and others elevated; such episodic elevations are consequential.

Depression and sleep disturbance

Source: Van Mill JG, et al. Insomnia and sleep duration in a large cohort of patients with major depressive disorder and anxiety disorders. *J Clin Psychiatry* 2010;71:239-246.

Both anxiety and depression disorders have a strong association with sleep disturbance. The association between sleep and depression is bidirectional: Depression is often manifest by or leads to sleep disturbance, and persistent insomnia increases risk of depression.

Van Mill et al sought to elucidate further the relationship between sleep disorders and depression by analyzing subjects in the Netherlands Study of Depression and Anxiety cohort (n = 2619).

In this population of subjects (approximately three-fourths suffered from depression and/or anxiety), almost half scored at least 9 on the Insomnia Rating Scale (IRS; the same metric that was employed in the Women's Health Initiative), fulfilling criteria for clinically significant insomnia. Insomnia scores were related to both anxiety and depression, but worse for depression, and highest for comorbid depression and anxiety. Interestingly, even persons with depression or anxiety in remission had elevated scores on the IRS. The authors suggest that, based upon their data, inquiry into sleep status is valuable not only during both depression and anxiety, but even during periods of remission.

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Atypical Fractures and Bisphosphonate Therapy

In this issue: Fractures and bisphosphonate therapy, warfarin anticoagulation and influenza vaccine and cotrimoxazole, antiplatelet therapy with clopidogrel and aspirin, FDA Actions.

Bisphosphonates and atypical fractures

Atypical fractures of the femur have been linked with bisphosphonate therapy in several recent news stories. A recent industry-sponsored study looks to quell these concerns. Secondary analysis from three large randomized bisphosphonate trials with more than 14,000 women showed that among 284 hip or femur fractures recorded, a total of 12 fractures in 10 patients were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient years. As compared with placebo, the relative hazard ratio for the three trials did not meet statistical significance, although confidence intervals were wide. The authors conclude that the occurrence of fracture of the subtrochanteric or diaphyseal femur was very rare even among women who had been treated with bisphosphonates for as long as 10 years (*N Engl J Med*; published on-line March 24, 2010). An accompanying editorial published on-line at the same time by Elizabeth Shane, MD, Columbia University, acknowledges that despite excellent safety profiles, bisphosphonates have been associated with "atypical" fractures of the femur that occur with minimal or no trauma, generally affecting the proximal third of the femoral shaft. Most of these fractures have occurred in women on long-term alendronate therapy, occasionally taken together with other antiresorptive drugs, corticosteroids, or proton pump inhibitors. Shane points out that while these fractures represent concern, they are uncommon and actually occur more frequently in patients who are not on bisphosphonates. The results of this study "provide assurance that subtrochanteric fractures are extremely rare" and many more hip fractures are "prevented by bisphosphonates than are potentially caused by the drugs." Treatment with bisphosphonates up to 10 years is more effective than shorter-term treatment in preventing new vertebral fractures and nonvertebral fractures, but she also suggests that patients should be considered for "drug holidays with careful observation" if they have been on long-term therapy.

Warfarin, flu vaccine, and cotrimoxazole

Anticoagulation with warfarin requires careful monitoring. Concomitant use of medications may result in changes in the international normalized ratio (INR), which may increase the risk of bleeding or decrease the effectiveness of therapy. Two studies in the April 12 issue of *Archives of Internal Medicine* clarify the risk of two commonly used medications, influenza vaccine and the antibiotic trimethoprim-sulfamethoxazole. Patients on warfarin have been told that they need careful monitoring after the influenza vaccine, although the effect is not clear. Some guidelines have suggested that flu shots prolonged INRs, while others suggest the vaccine reverses the anticoagulation effect.

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In this study, 104 patients on a stable warfarin regimen were randomized to receive influenza vaccine and subsequent placebo administration or vice versa. All patients were tested for coagulation variables and followed for clinical events. The influenza vaccine had no effect on anticoagulation compared to placebo. There were no fatal or major bleeding events. The authors conclude that the influenza vaccine has no significant effect on INR values or warfarin weekly doses in patients on chronic warfarin therapy and that close monitoring of INR values after influenza vaccine is not required (*Arch Intern Med* 2010;170:609-616).

Conversely trimethoprim-sulfamethoxazole (cotrimoxazole) may significantly prolong INRs with adverse clinical outcomes. In the population-based, nested case-controlled study using health care databases in Canada, residents 66 years or older who were treated with long-term warfarin were evaluated for upper gastrointestinal (GI) tract hemorrhage. Of the more than 134,000 patients on warfarin, 2151 patients were hospitalized for upper GI hemorrhage. Recent use of cotrimoxazole was almost four times more common in those hospitalized (adjusted odds ratio, 3.84; 95% CI, 2.33-6.33). The odds ratio for treatment with ciprofloxacin also was higher (1.94), but no significant association was observed with amoxicillin, ampicillin, nitrofurantoin, or norfloxacin. The authors conclude that among older patients receiving warfarin, cotrimoxazole is associated with a significantly higher risk of upper GI tract hemorrhage. Ciprofloxacin was also associated with risk and whenever possible clinicians should prescribe alternate antibiotics in patients receiving warfarin (*Arch Intern Med* 2010;170:617-621).

Clopidogrel and aspirin

What is the optimal duration of dual antiplatelet therapy with clopidogrel and aspirin in patients with drug-eluting stents? In previous studies, early discontinuation of dual antiplatelet therapy has been identified as a risk factor for late stent thrombosis. A new study seeks to determine whether dual antiplatelet therapy for more than 1 year is of value. In a study that merged data from two concurrent randomized, clinical trials, 2701 patients who had received drug-eluding stents and had been free of major adverse cardiac events, cerebrovascular events, or major bleeding for a period of at least 12 months were randomized to receive clopidogrel plus aspirin or aspirin alone. The primary endpoint was a composite of myocardial infarction (MI) or death from cardiac causes. The cumulative risk of the primary outcome at 2 years was 1.8% with dual antiplatelet therapy as compared with 1.2% with aspirin monotherapy (hazard ratio, 1.65; 95% confidence interval, 0.80-3.36; $P = 0.17$). The individual risks of MI, stroke, stent thrombosis, need for repeat revascularization, major bleeding, and death did not differ significantly between the two groups. However, there was a trend toward higher risk for these outcomes in the dual therapy group ($P = 0.051$ for MI, stroke, or death from any cause; $P = 0.06$ for MI, stroke, or death from cardiac cause). The authors conclude that use of dual antiplatelet therapy for longer than 12 months is not more effective than aspirin alone in patients who have received drug-eluding stents (*N Engl J Med* 2010; 362:1374-1382).

FDA Actions

Rifaximin, Salix Pharmaceutical's minimally absorbed (nonsystemic) oral antibiotic has been approved to reduce the risk of recurrent hepatic encephalopathy in patients with advanced liver disease. Rifaximin was previously approved to treat traveler's diarrhea. The drug, which is taken orally twice a day, appears to reduce ammonia levels by reducing gut flora. It is marketed as Xifaxan®.

The FDA has approved Pancreaze, a new pancreatic enzyme product for patients who do not produce enough pancreatic enzymes (due to cystic fibrosis, chronic pancreatitis, pancreatic surgery, etc.). Pancreaze is the third approved pancreatic enzyme product on the market after Abbott's Creon® and Eurand's Zenpep®. The approval coincides with the FDA's deadline to cease marketing unapproved pancreatic enzyme products that have been available for many years. In October 2007, the FDA announced a deadline of April 28, 2010, after which time unapproved products would no longer be available.

The FDA has approved the first generic version of the popular antihypertensive losartan (Cozaar®) as well as the combination of losartan and hydrochlorothiazide (Hyzaar®). This represents the first generic angiotensin receptor blocker on the market, a development that has been anxiously awaited by consumers. Losartan carries a boxed warning against using the drug during pregnancy. Generic losartan is available in 25 mg, 50 mg, and 100 mg strengths, while losartan/hydrochlorothiazide is available in 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg strengths.