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

ILLUSTRATIVE CASE SERIES

Hairy Cell Leukemia

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

A 51-YEAR-OLD MAN WAS BROUGHT TO THE EMERGENCY department with severe abdominal pain and hypotension. He had no known chronic medical disease but for the past few months had experienced a loss of appetite, weakness, and fatigue. Despite these symptoms, he had not missed work (electrical engineer). Over the six months, his weight had fallen from 190 to 175 pounds. He did not recall night sweats or fever, but did mention that he experienced a loss of appetite and occasional nausea. On two occasions during the prior week, he vomited.

Upon presentation to the emergency room, he was noted to have severe abdominal pain, particularly on the left side, was markedly pale, and there were petechiae over his trunk and upper and lower extremities. Blood pressure was palpable at 60 mm Hg (systolic), and his pulse was 140 and regular. His abdomen was distended, and bowel sounds were absent.

Laboratories revealed his hemoglobin was 6.3 g/dL, total white blood count was 1,500/uL, and platelet count was 45,000/uL. Computerized tomography obtained in the emergency room demonstrated an enlarged spleen, with apparent extravasation of contrast raising the likelihood of splenic rupture.

The patient was taken to the operating room where an enlarged spleen (850 gm) with two focal lacerations was removed. There was approximately

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1,100 cc of free blood within the abdominal cavity. Post-operative management was uneventful, and he was discharged on the 20th hospital day. At that time, his hemoglobin was 11.1 g/dL, WBC 3,800/uL, and platelet count 220,000/uL.

Pathology of the spleen revealed changes consistent with hairy cell leukemia (HCL), with diffuse involvement throughout the red pulp and, to a lesser extent, the white pulp. Peripheral blood immunophenotyping revealed the characteristic pattern of HCL (CD11c, CD25, CD103, CD123 and CD20). A bone-marrow biopsy obtained approximately one week prior to discharge revealed a generally fibrotic and hypocellular marrow with an infiltration of mononuclear cells that stained brightly with anti-CD20. The patient was referred for management of hairy cell leukemia.

DISCUSSION

Although, historically, splenectomy was the initial treatment for many patients with HCL, the success of current chemotherapeutic approaches precludes such an approach in the great majority of cases. Of course, in this case, surgery was life-saving and an effective initial treatment for his disease. The patient was fortunate to receive such prompt and aggressive management. From the data, as presented above, no immediate additional therapy would be warranted. Instead, the patient should be carefully followed with the expectation that, down the road, treatment will be required. Currently, there are no data that would indicate early intervention in cases such as this, or for patients with minimal residual disease (MRD), which translates to longer survival.

Before considering HCL-specific treatments, it is important to recognize that patients without a spleen are susceptible to bacterial infection and sepsis, and a strategy for vaccination and prophylactic antibiotics should be defined.[1]

The timing for initiating chemotherapy is not well established but, typically, intervention is warranted coincident with progressive cytopenias or the appearance of constitutional symptoms. Keeping in mind that the standard initial approach involves the use of purine nucleoside analogs, which themselves can be associated with granulocytopenia, treatment should begin before the granulocyte count falls to levels much below 2000/uL. Just as there is no consensus regarding the time to start therapy, there is none regarding initial treatment, other than the use of drugs in the purine nucleoside analog class and the need to attain a complete remission. The largest experience is with cladribine, and when administered by continuous infusion over seven days (0.1 mg/kg per day), complete remissions have been reported in over 90% of cases.[2,3] Comparable responses also have been observed in patients treated on intermittent schedules (e.g., daily dose for five days or weekly dose for six weeks),[4] or even when the drug is administered subcutaneously.[5] Another commonly used, and most likely equally successful, purine nucleoside analog is pentostatin. Whereas the most substantial data for cladribine is with the initial seven-day infusion, pentostatin is typically administered on an interrupted schedule (e.g., every two weeks), which involves more frequent office visits and a more protracted treatment phase but offers the advantage of being able to adjust doses on the basis of blood counts and renal function, thereby minimizing the risk for protracted cytopenias.[6]

HCL cells typically express CD20, and there is current interest in exploring a role for rituximab, either with a purine nucleoside analog in patients with relapsed disease or as a single agent for patients with MRD.[7,8] Also, interferon alpha is known to be effective, and newer immunological agents, such as the recombinant immunotoxins directed against CD25 (LMB-2) or against CD22 (BL22), hold promise for patients refractory to purine nucleoside analogs.

In summary, this patient was diagnosed with HCL at the time of emergency laparotomy for splenic rupture. Post-operatively, and for a yet-to-be defined period of time thereafter, he should be monitored closely. When the trajectory of his peripheral blood counts indicates impending risk, or as he develops constitutional symptoms, a purine nucleoside analog should be pre-

scribed. In this case, in light of his prior health and presumably normal renal function, I would favor a single course of cladribine rather than a more protracted course of pentostatin, although the latter offers more fine tuning with regard to the aversion of protracted cytopenias and is the approach I would take in older or more impaired patients. The likelihood of success is high but, upon relapse, a number of active drugs and biologics are currently available and offer an excellent chance for durable second or even third remissions. There is no definitive proof that the disease is curable, and treatment, when asymptomatic with minimal disease, remains in the domain of clinical research. ■

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RAPID REVIEW

Novel Therapies for Malignant Melanoma: A New Generation of High-affinity, Selective BRAF Inhibitors

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

Approximately 60% of human melanomas express a mutant form of the serine/threonine kinase BRAF, in which substitution of glutamic acid for valine at amino acid 600 (V600E) leads to the RAS-independent activation of the BRAF kinase. This constitutive activation of BRAF, with subsequent activation of the MEK1/2 and ERK1/2 kinases, promotes neoplastic features, including enhanced cell-cycle progression, resistance to apoptosis, changes in cell motility, and invasiveness, all of which, in combination with other genetic changes (e.g. those inhibiting cell senescence), define the pathogenesis of malignant melanoma. Recently, high-affinity, small-molecule inhibitors that specifically target BRAF have entered clinical trials and have shown exciting activity as single agents against mutant BRAF melanoma. These early-stage trials will be reviewed here, and new concepts of how BRAF inhibitors work in tumors with different genetic backgrounds will be discussed.

EARLY-PHASE CLINICAL TRIALS OF THE NEW GENERATION OF BRAF INHIBITORS

A phase I study of PLX4032 examining MTD, toxicity, and pharmacokinetic and pharmacodynamic endpoints enrolled 49 patients with metastatic melanoma, three with thyroid cancer, one rectal cancer, and one ovarian cancer, tumor types known to express V600E mutant BRAF.[1] PLX4032 had previously been shown to regress V600E-BRAF mutant tumors in human melanoma xenograft models with minimal toxicity to mice.[2]

The clinical trial utilized two different preparations of PLX4032 with different bioavailabilities, which complicated the dose escalation. Of the 12 metastatic melanoma patients treated with 240 mg BID or higher, seven had BRAF mutations; five of these patients experienced tumor regression, with one RESIST PR and one unconfirmed PR. Two of 5 pts with unknown BRAF status had regression (one confirmed PR). All seven patients with tumor regression were still in remission 4-14 months after treatment. Three thyroid patients had minimal regression (9%-16%) and remained stable for 4-7 months at the time of the report. The MTD was 720 mg PO BID, although the intermediate dose of 960 mg remains to be tested. Dose-limiting toxicities consisted of rash and fatigue. The preliminary conclusion of this ongoing trial was that PLX4032 was active against BRAF-mutant melanoma and was well tolerated.

GSK2118436 is a potent, selective ATP competitive inhibitor with 100-fold greater activity against mutant vs. wild-type BRAF, which had demonstrated tumor regression in a melanoma xenograft model. Sixty-one patients (52 with mutant BRAF) were treated in a phase I study. At the time of abstract presentation, the MTD had not been reached.[3] In patients with mutant BRAF melanoma, 18 of 30 had > 20% tumor response by RESIST criteria at the first evaluation, 8-9 weeks after beginning treatment. The preliminary conclusion was that this agent has clinically significant antitumor activity with minimal toxicity.

Plexxikon, Inc., in partnership with Roche, is sponsoring the BRIM3 (BRAF Inhibitor in Melanoma) phase III, randomized study in which 700 previously untreated melanoma patients will receive either PLX4032 at a dose of 960 mg BID or dacarbazine (DTIC). The primary endpoint is overall survival, and secondary endpoints include duration of response, progression-free survival, and best overall response rate. BRIM3 is being conducted at 100 sites in the United States, Canada, Australia, and Europe. A second study, BRIM2, will study the efficacy of PLX4042 in 100 previously treated melanoma patients whose tumors express mutated BRAF.

MECHANISMS OF BRAF-INHIBITOR ACTIVITY: CURRENT HYPOTHESES AND FUTURE DIRECTIONS

In vitro, BRAF inhibitors effectively inhibit proliferation of BRAF-mutant cell lines, but have no activity against melanoma cells expressing a mutant NRAS oncogene.[4,5] Importantly, recent studies indicate that, under some circumstances, BRAF inhibitors can activate the RAF-MEK-ERK pathway.[6] How can one explain the paradoxical activation of BRAF by a BRAF inhibitor, and how does this alter the way clinicians utilize these novel compounds to treat patients with tumors that may encode mutant BRAF?

An important facet in understanding Raf biology was the discovery that Raf molecules exist as side-to-side dimers (either as homodimers or heterodimers of CRAF and BRAF).[7] Additionally, it was shown that paradoxical activation of RAF dimers by BRAF inhibitors requires an activated RAS. Thus, paradoxical MAPK activation only occurs when BRAF is inhibited in the presence of oncogenic RAS. The molecular mechanisms by which BRAF inhibitors activate the MAPK pathway remain to be definitively explained. One provocative experiment suggests that inhibitor binding to the ATP-binding site of one partner of a dimer can induce the transactivation of kinase activity of the other partner.[8] In this study, a CRAF with an inactivated kinase domain (generated by in vitro mutagenesis) was dimerized to a different CRAF mutant that could not bind the BRAF inhibitor. When introduced into cells, the addition of a BRAF inhibitor led to activation of the kinase of the second mutant CRAF, indicating that inhibitor binding to the kinase-dead CRAF had activated the kinase of its partner.

Realizing that mutant BRAF and activated, oncogenic RAS do not coexist in the same melanoma, it becomes clear that paradoxical BRAF activation by BRAF-specific inhibitors can only occur in those subsets of melanoma patients whose tumor harbors activated NRAS (but not mutant BRAF). Furthermore, there are experimental data in a murine transgenic mouse model that kinase-dead BRAF (mimicking the situation in patients taking BRAF inhibitors) can enhance the in vivo tumorigenicity of mutant NRAS.[5] This suggests that BRAF inhibitors may actually enhance the growth of human melanomas harboring NRAS mutations, and that they should not be used in this situation. Hence, the BRAF and NRAS genotypes of a patient's tumor should be known before they are treated with BRAF-selective inhibitors. One way to avoid this would be to combine BRAF inhibitors with MEK inhibitors, with the latter precluding a paradoxical activation of the MAPK pathway. In fact, a new phase I/II study will combine GSK2118436 with a MEK1/2 inhibitor GSK1120212 in patients with

BRAF-mutant malignant melanoma. However, it is unclear why the MEK inhibitor is needed in this situation where the tumor cells are known to express mutant BRAF, since the model indicates that paradoxical activation of RAF by BRAF inhibitors requires mutant RAS, which will not be present in BRAF-mutant melanomas; this combination of drugs would seemingly eliminate the specificity of targeting mutant BRAF and would introduce the toxicities associated with MEK inhibitors that are not targeted to the tumor.

While much remains to be learned mechanistically, it is clear that the new generation of potent BRAF inhibitors have important clinical activity against BRAF-mutant melanoma, and it will be of great interest in the years to come to follow their clinical development as they are combined with standard chemotherapeutic agents as well as small molecule inhibitors of other signal transduction pathways. ■

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ABSTRACT & COMMENTARY

The Saga of Fruit/Vegetable Consumption and Cancer Risk

William B. Ershler, MD

Synopsis: *In an analysis of a European cohort of approximately 400,000 individuals, among whom 30,000 cancers developed over nine years of follow-up, a very small inverse association between intake of total fruits and vegetables and cancer risk was observed.*

Source: Boffetta P, et al. Fruit and vegetable intake and overall cancer risk in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst.* 2010;102:529-537.

It is a common notion that much cancer can be prevented by high intake of fruits and vegetables. The initial enthusiasm for such risk reduction was based upon early case-control studies, which were sufficient enough for the World Health Organization to formally recommend people to eat at least five portions (approximately 400 g) of fruits and vegetables daily.[1] Subsequently, inconsistent results from many studies have not been able to conclusively establish an inverse association between fruit and vegetable intake and overall cancer risk. Prior to the current report, there had been six relatively large prospective studies examining this question.[2-7] Of these, one showed that mortality was lower in both men and women when higher amounts of green and yellow vegetables and fruits were consumed;[7] three studies reported a lower incidence of cancer in women who had high intakes of fruit and vegetables;[2,3,5] and two showed no association between cancer risk and fruit or vegetable intake.[4,6]

To provide additional, substantial data on the relationships between total intake of fruits, total intake of vegetables, or total intake of both fruits and vegetables in combination and cancer risk, Boffetta and colleagues conducted an analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Detailed information on the dietary habit and lifestyle variables of the cohort during the years 1992-2000 was obtained. Cancer incidence and mortality data were ascertained, and hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox regression models. Analyses also were conducted for cancers associated with tobacco and alcohol after stratification for tobacco smoking and alcohol drinking.

Of the initial 142,605 men and 335,873 women from ten European countries included in the EPIC cohort, 9,604 men and 21,000 women were identified with cancer after a median follow-up of 8.7 years. The crude cancer incidence rates were 7.9 per 1,000 person years in men and 7.1 per 1,000 person years in women. Associations between reduced cancer risk and increased intake of total fruits and vegetables combined and total vegetables for the entire cohort were similar (200 g/d increased intake of fruits and vegetables combined, HR = 0.97, 95% CI = 0.96 to 0.99; 100 g/d increased intake of total vegetables, HR = 0.98, 95% CI = 0.97 to 0.99); intake of fruits showed a weaker inverse association (100 g/d increased intake of total fruits, HR = 0.99, 95% CI = 0.98 to 1.00). The reduced risk of cancer associated with high vegetable intake was restricted to women (HR = 0.98, 95% CI = 0.97 to 0.99). Stratification by alcohol intake suggested a stronger reduction in risk in heavy drinkers and was confined to cancers caused by smoking (cancers of the lung, kidney, upper respiratory and gastrointestinal tracts, liver, stomach, pancreas, and bladder) and alcohol (upper respiratory and gastrointestinal tracts, breast, liver, and colorectum).

■ COMMENTARY

During the 1980s and early 1990s, there emerged enthusiasm for the cancer-protective effects of fruits and vegetables, based primarily on case-control studies suggesting a substantial risk reduction among those who consumed high levels of fruits and vegetables. In fact, the World Health Organization recommended that people eat at least five portions (approximately 400 g) of fruits and vegetables daily.[1] However, case-control studies have been prone to a number of biases, and when subjected to prospective analysis, a much smaller effect, if any, had been observed.[2-7] The current study, by far the largest on the topic, demonstrated a very small inverse association between the intake of total fruits and vegetables and cancer risk. As noted, vegetable consumption alone conferred a modest benefit, but this was restricted to women, and consumption of fruits/vegetables by heavy drinkers had a small reduction in those cancers caused by smoking and drinking.

Willett, in an accompanying editorial,[8] concludes that this study confirms that fruit and vegetable consumption, in general, has little or no effect on cancer risk, although the benefits, with regard to protection from cardiovascular disease, is more substantial. He also suggests that, whereas total fruit/vegetable consumption is of marginal value, certain individual dietary components may be of benefit and should be studied separately. ■

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ABSTRACT & COMMENTARY

Gemcitabine-Capecitabine for Advanced Breast Cancer: Impressive Phase II Results

William B. Ershler, MD

Synopsis: *In a phase II trial of capecitabine and gemcitabine for patients who had previously received an anthracycline for either as an adjuvant or for metastatic disease, overall response rate was 55% and the median time to progression was 11 months. These results were somewhat better for patients who were being treated for the first time for advanced disease (i.e., for recurrence after adjuvant therapy) when compared to those who were receiving the drugs as second line.*

Source: Ciruelos EM, et al. Gemcitabine and capecitabine in previously anthracycline-treated metastatic breast cancer: A multicenter phase II study (SOLTI 0301 trial). *Annals Oncol.* 2010;**21**:1442-1447.

Anthracyclines have assumed a primary role in the management of breast cancer, and are currently used as initial therapy either in the adjuvant or metastatic setting. Thus, clinicians frequently encounter the need to treat anthracycline-pretreated patients, and defining optimal therapy in this setting remains to be established.[1] Certainly, taxanes are commonly used in anthracycline-pretreated breast cancer patients, but other agents, such as 5-fluorouracil (F-FU), vinorelbine, capecitabine, and gemcitabine also are known to have activity. Capecitabine, an orally administered prodrug of 5-FU, when used first line as a single agent for patients with advanced disease, has demonstrated response rates ranging from 25-37%.[2] Similarly, gemcitabine, a pyrimadine analogue of deoxycytidine, has demonstrable activity when used in the setting of metastatic breast cancer.[3] In preclinical studies, when these two drugs are used together, a synergistic anti-tumor effect has been demonstrated.[4] Furthermore, several phase II studies have been conducted demonstrating the safety and efficacy of this combination in a wide range of tumors including, most notably, pancreatic cancer.[5] In fact, in a retrospective report of 31 heavily pretreated breast cancer patients, an overall response rate of 10% was observed,[6] whereas in a phase II trial (also in heavily pretreated patients), the overall response rate was 48.7% and the median time to progression was five months .

To study this combination further, Ciruelos and colleagues throughout Spain carried out a multicenter, phase II clinical trial on the combination of gemcitabine and capecitabine in advanced anthracycline-pretreated breast cancer patients. This was an open-label, multicenter, non-randomized, phase II trial, with the primary objective to assess overall response rate and, secondarily, to estimate time to progression, duration of response, and safety.

The study was empowered to analyze two groups: group 1, not previously treated for metastatic disease; and group 2, previously treated. A total of 76 anthracycline-pretreated breast cancer patients were enrolled — 41 in group 1 and 35 in group 2.

Patients received gemcitabine 1000 mg/m^2, i.v., as 30 min-infusion on days 1 and 8 every 21 days, and oral capecitabine 830 mg/m^2 b.i.d., days 1–14 every 21 days. This dose and schedule was chosen on the basis of a prior study.[7]

The overall response rate was 61% for group 1, 48.5% for group 2, and 55.2% for the whole population. The tumor control rate (defined as the sum of overall response plus stable disease rates) was 73% for group 1, 80% for patients in group 2, and 76% for all patients. Median time to progression was 13.0 months for group 1, 8.2 months for group 2, and 11.1 months for the whole population. Most frequent grade 3–4 observed toxicities were neutropenia (60%), asymptomatic liver toxicity (13.5%), asthenia (14%), and hand–foot syndrome (16%). Only one patient presented with febrile neutropenia. No treatment-related deaths occurred. Dose delays or reductions occurred in approximately 20% of cycles, primarily because of neutropenia (most commonly at day eight of any cycle) or hand-foot syndrome.

■ COMMENTARY

Thus, the combination of gemcitabine and capecitabine is an active and safe regimen in anthracycline-pretreated breast cancer patients. Although

this was not a randomized study, the response rates are quite similar to the combination of docetaxel with capecitabine.[8] Also, the safety and toxicity were quite reasonable, even though there was quite a high rate of dose and schedule change. A randomized trial is in order to determine whether this regimen is actually superior to one that is taxane-based in terms of response or tolerability. Furthermore, for those patients with tumors that over-express HER-2, it is unclear to what degree the addition of trastuzumab to either of these regimens would influence the overall success of therapy. ■

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CME Questions

4. For patients with breast cancer recurrence after receiving an anthracycline for adjuvant therapy, the combination of gemcitabine and capecitabine is likely to produce a progression-free survival (based upon the recently published Phase II report) of:

a. 3 months
b. 6 months
c. 12 months
d. 18 months

5. Daily consumption of 200 g of fruit and vegetables was demonstrated in the EPIC cohort to be associated with:

a. a risk reduction of 35% in cancer development.
b. a small (2-4%) but statistically significant reduction in cancer development.
c. a small (0-1%) but statistically insignificant reduction in cancer development.
d. no effect on the risk for cancer development.

6. Recently, high-affinity, small-molecule inhibitors that specifically target BRAF have entered clinical trials and have shown exciting activity as single agents against mutant BRAF melanoma. Approximately what percentage of patients with melanoma have mutant forms of the BRAF gene and would, therefore, be candidates for this targeted therapy?

a. more than 90%
b. 60%
c. 25%
d. 5%

Answers: 4. (c); 5. (b); 6. (b)

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;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

[IN FUTURE ISSUES]

Erlotinib Maintenance for Patients with Advanced NSCLC

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Dietary added sugar and lipids

Source: Welsh JA, et al. *JAMA* 2010;303:1490-1497.

Processed foods often contain added sucrose or high-fructose corn syrup to enhance palatability. Such added sugars (aSUG) may comprise as much as 16% of Americans' caloric intake. The Institute of Medicine suggests a 25% maximum of daily calories from aSUG and the American Heart Association suggests a 5% maximum. The incidence of obesity, diabetes, and dental caries is associated with increased aSUG, but the relationship between aSUG and lipids is less well-defined.

Welsh et al studied the relationship between aSUG and lipids in NHANES participants (n = 6113). Overall, approximately 16% of calories daily were supplied by aSUG in this population of adults. Excluded from analysis were persons with dietary reports that appeared unreliable (e.g., < 600 calories/d), marked triglyceride elevation, BMI > 65 kg/m^2, and those taking cholesterol-lowering medications.

There was a statistically significant association between progressively higher levels of aSUG and lower HDL. Similarly, LDL and triglyceride levels were linearly related to aSUG, although the LDL results were not statistically significant in men.

The mechanism(s) by which aSUG consumption is related to lipid levels is incompletely understood, although it is recognized that fructose may stimulate hepatic lipid production and reduce peripheral lipid clearance. Although not demonstrated in a clinical trial, conceptually, reductions in aSUG on a population-wide basis could have important public health benefits. ■

Underrecognition of adverse effects

Source: Zimmerman M, et al. *J Clin Psychiatry* 2010;71:484-490.

The design of clinical trials sometimes allows for failed detection of adverse effects related to medication. Perhaps the most widely recognized disconnect is in relation to ACE inhibitors: Prescribing information suggests a very low incidence of cough (typically < 10%), yet clinical experience suggests twice that frequency. The primary reason for this incongruence is that most side effects are passively reported; for a variety of reasons, patients may fail to spontaneously report adversities that could be related to medication.

Zimmerman et al addressed this issue among depressed outpatients treated with a variety of antidepressants and anxiolytics. Subjects were seen by board-certified psychiatrists, and after their office visits, filled out questionnaires addressing adverse effects possibly related to medication.

Over a 6-week interval, more than 25% of the 2233 reported side effects occurred at least daily, but fortunately, the majority were rated low on the severity scale. Only about 20% of individuals rated adverse effects as 4-5 on a 5-point scale.

Overall, 20 times more adverse effects were identified by questionnaire than in psychiatrists' records. Comparison limited to either highly frequent or bothersome adverse effects still found that questionnaires identified 2-3 times as many adversities as clinicians had recorded.

A number of explanations can clarify some of this discrepancy: Psychiatrists may not record all adverse effects they see, patients may not report all issues that bother them (or minimize the bother), and some adverse effects may be so anticipated that their presence does not merit specific notice. In any case, it appears that patients shoulder a much higher level of adverse effect burden when treated for depression than would be readily apparent from review of their clinical records. ■

Female sexual dysfunction in diabetes

Source: Esposito K, et al. *Int J Impot Research* 2010;22:179-184.

Male sexual dysfunction is well recognized as a consequence of diabetes. Currently, there are no approved medications for treatment of female sexual dysfunction (FSD), though epidemiologic surveys suggest that the population prevalence of FSD rivals that of male sexual dysfunction. FSD is typically categorized as either disorders of desire, arousal, orgasm, or pain. Of course, FSD subcategories are commonly comorbid.

This study recruited adult type 2 diabetic women (mean age, 58 years) attending a clinic in Italy for routine care of diabetes to complete the Female Sexual Function Index, a validated instrument for assessing FSD.

Overall, the prevalence of FSD in the entire population was 53%. This is similar to, but even greater than, the prevalence reported in two large population surveys (both with broader age range, and not limited to diabetics), which indicated an FSD

prevalence of 43%. FSD was 30% more frequent in postmenopausal women than premenopausal women and was associated with depression. The only recognized protective factor was physical activity.

The etiology of FSD in diabetes is unclear, and may include vascular, neurologic, and endocrinologic factors. The high prevalence of FSD in diabetic women should motivate clinicians to be more proactive in its identification. ■

Vitamin D from the sun or supplements?

Source: Terushkin V, et al. *J Am Acad Dermatol* 2010;62:929.e1-9.

While I cannot speak for you, my recent experience is that under every rock I overturn is a vitamin D-deficient patient. At least that's what checking 25-OH vitamin D levels (the currently recommended test for vitamin D status) suggests. Should we recommend sun exposure, supplements, or both to address hypovitaminosis D?

Terushkin et al compared the amount of sun exposure necessary to provide the same plasma vitamin D levels as a 400 IU/d vitamin D supplement. They chose to study individuals in Miami, FL, and Boston, MA. Of course, sun exposure varies depending upon geography and season, as well as skin type. In July, the amount of sun time to provide as much systemic vitamin D as 400 IU orally was the same in both cities (3 min at 12 noon). A darker-skinned individual would require 5 min.

During winter months, there were marked differences in required exposure time. In Miami, 6 min of sun vs 23 min of sun in Boston would be required. Since most individuals do not expose 25% of the body surface (the face is only 3.5%) to sun during the winter in cities like Boston, a correspondingly greater time exposure would be required … an unlikely scenario.

Because of the concern about sun exposure and its relationship to photoaging and skin cancer, as well as the neglect of optimum sunscreen utilization, the authors of this article favor vitamin D supplementation over sun exposure as the safest way to maintain vitamin D adequacy. ■

Exenatide + rosiglitazone added to metformin

Source: DeFronzo RA, et al. *Diabetes Care* 2010;33:951-957.

It is widely recognized that approximately half of beta-cell function (BCF) has been lost by the time type 2 diabetes (DM2) is diagnosed. Additionally, it appears that despite vigorous treatment, loss of BCF continues inexorably.

The most recently published treatment algorithm for DM2 management by the ADA suggests that initial therapy should be lifestyle with metformin, unless a specific contraindication to metformin exists. Over time, however, most patients will require augmentation of treatment.

Exenatide (EXE) and rosiglitazone (ROS) are effective therapies for glucose control and work by complementary mechanisms of action. Additionally, sometimes thiazolidinedione therapy is compromised by weight gain, but since exenatide consistently provides weight loss, their combination is clinically sensible.

DM2 subjects already on treatment with lifestyle plus metformin (n = 101) were randomly assigned to add-on therapy with EXE alone, ROS alone, or EXE + ROS, and followed for 20 weeks. BCF was measured by the glucose disposition index.

In addition to the anticipated reduction in A1c by polypharmacy, EXE + ROS provided significant improvements in insulin secretion and overall BCF. Long-term studies are necessary to discern whether these favorable effects can be sustained and translated into risk reduction for macro- and/or microvascular outcomes. ■

Intensive BP control in diabetes

Source: Accord Study Group. *N Engl J Med* 2010;362:1575-1585.

Because it is recognized that type 2 diabetics (DM2) incur greater risk of CV outcomes than the general population, consensus groups have advocated BP < 130/80 mmHg as a preferred goal, in contrast to 140/90 mmHg for the general hypertensive population. Despite enthusiasm for this posture, and essentially global advocacy for the concept that lower is better in diabetes, no prospective, randomized trial has been done that confirms such benefits. The ACCORD trial was designed to compare CV outcomes achieved with tight BP control (SBP < 120 mmHg) vs standard therapy (SBP < 140 mmHg). The ACCORD trial had several limbs, including a glucose control and a lipid control arm, which were not addressed in this publication.

Almost 5000 diabetics were randomly assigned to intensive BP vs standard BP treatment and followed for the primary endpoint of (composite) nonfatal MI and stroke, or CV death over a mean 4.7-year follow-up.

The tight control arm managed to achieve an SBP of 119.3 mmHg, compared to the standard treatment group SBP of 133.5 mmHg; of course, the number of medications required to attain control was substantially greater in the tight control group (3.4 drugs vs 2.3 drugs). Intensive BP lowering did not reduce the primary endpoint. Intensive BP control was associated with more adverse events.

No hypertension guidelines have been issued since the publication and promulgation of the ACCORD BP trial. Expert opinions vary in interpretation of this outcome. I have suggested that, in the absence of proven benefit by greater BP lowering, achievement of < 140/90 mmHg now represents a reasonable goal until further literature suggests otherwise. ■

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Aggressive Modification of Cardiovascular Risk Factors

In this issue: Aggressive approach to CVD reduces MI, folic acid and vitamin B12 for CAD, corticosteroids for acute exacerbations of COPD, prescription drug abuse among young adults, and ARBs and cancer risk.

CVD decreases with aggressive treatment

Aggressive modification of cardiovascular risk factors seems to be paying dividends, at least for a large population of insured patients in Northern California. In an analysis of nearly 18.7 million patient-years between 1999 and 2008, the rate of myocardial infarction (MI) increased in 1999 and 2000 and then decreased significantly every year thereafter (287 cases/100,000 person-years in 2000, decreasing to 208 cases/100,000 person-years in 2008; 24% relative decrease over the study period). The rate of ST-segment elevation MI decreased over the study period (133 cases/100,000 person-years in 1999 to 50 cases/100,000 person-years in 2008; $P < 0.001$) and the 30-day mortality rate decreased from 1999 to 2008 as well (adjusted odds ratio, 0.76; 95% confidence interval, 0.65-0.89). This occurred despite more aggressive diagnosis of MI.

The authors conclude, "The lower incidence of myocardial infarction — particularly ST-segment elevation myocardial infarction — is probably explained, at least in part, by substantial improvements in primary-prevention efforts, …" including statins and aggressive blood pressure reduction, as well as use of cardioprotective medications such as aspirin (*N Engl J Med* 2010;362:2155-2165).

An accompanying editorial points out that while these trends are generally the case in the United States, there are significant geographic differences. "The risk among residents of Oklahoma, the lower Mississippi corridor, and Appalachia, for example, is double that among other Americans, … " suggesting socioeconomic factors play a role. Hypertension and diabetes rates have increased slightly over the last decade, while smoking rates have decreased. Perhaps even more importantly, statin use has increased significantly (among those between age 45 and 64 years, statin use in men increased from 2.5% to 16.8% and from 1.9% to 13.5% in women; among those 65 years of age or older, statin use increased from 1.9% to 38.9% in men and from 3.5% to 32.8% in women). Aspirin, beta-blockers, and ACEIs/ARBs have also contributed to the decline in cardiovascular mortality in the United States (*N Engl J Med* 2010;362:2150-2153). ■

Folic acid and vitamin B12 for CAD

Unfortunately, lowering homocysteine with folic acid and vitamin B12 does not seem to be a benefit to patients with coronary artery disease. In a study from the United Kingdom, more than 12,000 survivors of myocardial infarction were randomized to 2 mg folic acid plus 1 mg vitamin B12 daily vs matching placebo, with the main outcomes being first major vascular event such as coronary event, stroke, or noncoronary revascularization. Folate and vitamin B12 were effective at reducing homocysteine levels by 28%; however, there was no difference in the rate of major vascular events over the 6.7 years of follow-up (25.5% active treatment vs 24.8% placebo; $P = 0.28$). Individually, there was no effect on major coronary events, stroke, or noncoronary

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revascularizations, nor was there a survival benefit from active treatment. Interestingly, the authors also looked at incidence of cancer and found no difference in that outcome either. The authors conclude that long-term reductions in blood homocysteine levels with folic acid and vitamin B12 do not have a beneficial effect on vascular or cancer outcomes (*JAMA* 2010;303:2486-2494). ■

Corticosteroids for exacerbations of COPD

Giving corticosteroids orally in lower doses is as effective as giving the drugs intravenously at higher doses for the treatment of acute exacerbation of COPD (ae-COPD), according to a recent study in the *Journal of the American Medical Association*. The records of nearly 80,000 patients in more than 400 hospital admissions for ae-COPD who received steroids were reviewed. The primary outcomes were treatment failure, defined as the initiation of mechanical ventilation, inpatient mortality, or readmission within 30 days. The vast majority of patients (92%) received IV steroids. After multivariate adjustment, the death rate was similar in the two groups (1.4% IV therapy vs 1.0% oral) and the composite outcome was also similar (10.9% IV vs 10.3% oral). In a propensity-matched analysis, the risk of treatment failure was actually significantly lower among orally treated patients (odds ratio, 0.84; 95% confidence interval, 0.74-0.95), as was the length of stay and cost. Of the orally treated patients, 22% were switched to IV therapy later in the hospitalization.

The authors conclude that for patients admitted for ae-COPD, low-dose steroids administered orally are as effective, and may be safer, than higher-dose IV steroids (*JAMA* 2010;303:2359-2367). An accompanying editorial suggests that rather than doing large non-inferiority studies to confirm these findings, sufficient evidence exists to change practice now with continued comparative effectiveness research via linked registries (*JAMA* 2010;303:2409-2410). ■

Prescription drug abuse in young adults

Prescription drugs are the new drugs of abuse among young adults. While drug use in general seems to be dropping in high schools, prescription drug abuse is skyrocketing. The recently published National Youth Risk Behavior Survey from the Centers for Disease Control and Prevention (CDC) showed that 1 of 5 high school students in the United States reported abusing a prescription drug at some time in their lives. The most commonly mentioned drugs were OxyContin®, Percocet®, Vicodin®, Adderall®, Ritalin®, and Xanax®. Prescription drug abuse was most common among white students (23%), followed by Hispanic students (17%), and then black students (12%). Not surprisingly, high school students were most likely to abuse drugs in their senior year (*MMWR* 2010;59:1-142). While many teens get their prescription drugs from medicine cabinets of family and friends, others order them online, and recently many drug dealers have begun specializing in prescription drugs.

Many young adults, however, seek opioids and benzodiazepines from physicians, especially in emergency departments (ED). A new report from *MMWR* reports that ED visits for nonmedical use of opioid analgesics increased 111% from 2004 to 2008 and increased 29% from 2007 to 2008 alone. The highest number of ED visits was recorded for oxycodone, hydrocodone, and methadone. ED visits for benzodiazepines also increased 89% over the same period. In 2008, the rates of visits for both opioids and benzodiazepines increased sharply after age 17 and peaked in the 21-24 year age group. During the 2004-2008 study period, the largest increase in ED visits to obtain drugs occurred among persons age 21-29 years. Findings were from the CDC and the Substance Abuse and Mental Health Services Administration, reviewing data from the Drug Abuse Warning Network (*MMWR* 2010;59:705-709). ■

ARBs and cancer risk

Do angiotensin receptor blockers (ARBs) increase the risk of cancer? In a widely reported study, researchers from Case Western Reserve performed a meta-analysis of 5 trials for which cancer data were available from more than 61,000 patients. Telmisartan was the ARB used in nearly 86% of the studies. Patients randomly assigned to receive ARBs had a rate of new cancer occurrence of 7.2% vs 6.0% for placebo (relative risk [RR], 1.08; 95% confidence interval [CI], 1.01-1.15; $P = 0.016$). The risk ratio was higher when the analysis was limited to trials where cancer was the prespecified endpoint (RR, 1.11; 95% CI, 1.04-1.18; $P = 0.001$). There was no difference in the rate of cancer deaths between the two groups. The authors conclude that this trial suggests that ARBs are associated with a modestly increased risk of new cancer diagnosis, but it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug and further research is warranted (*Lancet Oncology* 14 June 2010; early online publication). ARBs are involved in the regulation of cell proliferation, angiogenesis, and tumor progression, which are possible mechanisms for these findings. ■