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INSIDE

The Value of Post Adjuvant Chemotherapy Screening in Colorectal Cancer Patients

ABSTRACT & COMMENTARY

Synopsis: *In an analysis of important clinical outcomes after adjuvant chemotherapy for stage II and III colorectal cancer, Chau and colleagues from the United Kingdom reviewed the experiences of 530 patients. Of these, 154 relapsed with metastatic disease, local recurrence, or metachronous tumor. Routine screening (including CEA and CT scans) detected disease recurrence in more than half of those that were to recur, and, for these individuals, survival was superior to those who were discovered to have relapse on the basis of symptoms. The report supports the common practice of scheduled post chemotherapy screening for patients with colorectal cancer.*

Source: Chau I, et al. *J Clin Oncol*. 2004;22:1420-1429.

Nearly 40% of patients with colorectal cancer (CRC) experience disease relapse, despite potentially curative surgery.[1] For patients with resected stage II or III CRC, the primary objectives of follow-up are to detect either resectable metastases confined to the organs (ie, lungs or liver), resectable local recurrences, or metachronous cancer. However, the value of this follow-up has been highly debated. Chau and colleagues from the Royal Marsden Hospital in the United Kingdom evaluated the role of routine serum carcinoembyonic antigen (CEA) measurement and computed tomography (CT) as follow-up policy, and their impact on survival in adjuvant chemotherapy treated patients who developed disease recurrence or metachronous primary CRC. Following chemotherapy, patients were seen in the outpatient clinic every 3 months for the first year, every 6 months for the second year, and annually from then on. Serum CEA was measured at each clinic visit and CT scans of the thorax, abdomen, and pelvis were performed 12 months and 24 months following the end of chemotherapy.

The median follow-up of the 530 recruited patients was 5.6 years, with disease relapses occurring in 154 patients. Also, 42% (n = 65) of these relapses were detected by symptoms, 29% (n = 45) by CEA, 32% (n = 49) by CT and 6% (n = 9) by other methods, such as colonoscopy. Of the 49 patients in whom relapses were

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detected by CT, 14 had associated elevated CEA and were included in both the CEA and CT-detected groups. Therefore, 71% (n = 35) of the asymptomatic patients in the CT-detected group had normal CEA and their relapses could not have been identified separately from the CT. In addition, survival after relapse for the CT group was greater than that of the symptomatic group (P = .0046). Thirty three patients (21%) underwent surgery for relapse and had a better survival than those who did not (P = .00001). Only 2 patients from the symptomatic group underwent hepatic or pulmonary metastatic resection vs 13 from the CT group and eight from the CEA group (CT vs symptomatic, P < .001; CEA vs symptomatic, P = .015). Therefore, surveillance CT and CEA are valuable methods of follow-up after adjuvant chemotherapy in stage II and III colorectal cancer.

COMMENT BY WILLIAM B. ERSHLER, MD

In this analysis, of the 154 patients who relapsed after adjuvant chemotherapy for CRC, the discovery of recurrence was, as might be expected, earlier for those who had their disease detected by CT or rising CEA. Thirty three of the 154 were discovered early enough to proceed directly to potentially curative resections, but only 2 of these 33 were discovered to have recurrent disease on the basis of symptoms. Although the implications of this analysis support the common practice of routine surveillance of asymptomatic patients after adjuvant chemotherapy, a more skeptical interpretation might be that patients with more aggressive disease will progress to symptomatic disease within the 3- (for CEA) or 12-month (for CT) intervals, and these patients would be expected to have poorer survival. Thus, the screening might be more apt to discover those with more indolent tumor growth patterns. Perhaps a prospective randomized study could be constructed that examined more intensive screening (eg, monthly CEAs and semiannual CT scans) with the more conservative approach taken by Chau et al. Furthermore, the duration of post-adjuvant chemotherapy treated CRC patients remains an issue that needs clarification. ■

Reference

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Restaging Surgery for Women with Borderline Ovarian Tumors: Results of a French Mulitcenter Study

ABSTRACT & COMMENTARY

Synopsis: *Women who initially were diagnosed with Stage IA disease and who had serous borderline tumors or underwent cystectomy appeared to derive the most benefit from restaging surgery. Nonetheless, the indications for restaging surgery remain controversial, as no difference in recurrence rate was observed between women who underwent restaging and those who did not.*

Source: Fauvet R, et al. *Cancer*. 2004;100:1145-1151.

BORDERLINE OVARIAN TUMORS ACCOUNT FOR ABOUT 10-20% of all ovarian epithelial tumors and are characterized by occurrence in younger women, earlier stage at diagnosis and better prognosis compared to invasive ovarian cancer. In some cases, the diagnosis is

made after surgery, where neither complete ovarian resection (conservative operation) nor complete surgical staging information has been obtained, leaving the clinician in a quandary as to the appropriate next step. Fauvet and colleagues attempt to address this clinical situation through a review of all ovarian borderline or low malignant potential (LMP) tumors of the ovary diagnosed in their hospital system over a 12-month period. The principle aims of this retrospective review were to determine if conservative surgery was detrimental, if incomplete staging warrants a restaging operation, and what risk factors are associated with upstaging. Although no centralized pathological review of the individual cases was made, adherence to the current FIGO recommended classification scheme was followed. Three-hundred-sixty women with an ultimate final diagnosis of LMP tumor were accessioned. Of these, 150 or 42% underwent intraoperative histologic examination from which 97 (65%) were correctly identified as having LMP tumors. The remainder were classified as either benign (23%), carcinoma (2%) or not definitive (11%). Using Fauvet et al's definition of staging (to include peritoneal cytology and biopsies, omentectomy and, in the case of mucinous tumors, appendectomy), 37 women (38%) underwent complete evaluation. In this cohort, just 5 were treated conservatively defined as leaving the uterus and at least part of an ovary behind. Among the staged group, an additional 25 high-risk patients were added, as they underwent the formal staging procedure despite having inconclusive intraoperative histology.

In this cohort, one additional patient was treated conservatively, leaving 6 of 62 patients treated conservatively. Of the 298 incompletely staged or unstaged patients, 54 (18%) underwent a re-staging procedure. Although *a priori* criteria for re-staging was not discussed or presented, patients undergoing the procedure were significantly younger and more likely to have had an initial conservative procedure. Interestingly, only half of those women undergoing a second procedure actually met Fauvet et al's criteria of staging. However, the majority of those undergoing a second operation were done so with conservation of fertility as a goal (n = 48; 89%). Of these 54 secondary operations, more advanced disease was identified in 8 patients (15%), with 3 upstaged to stage IB, 1 to stage IIA, 1 to stage IIB, 2 to stage IIIA and 1 to stage IIIC. With the exception of the latter, they were all initially stage IA.

No significant characteristics were associated with upstaging although these tumors were more often serous and in women who had a cystectomy as a primary operation. At a median follow-up of 37 months, overall survival was nearly identical between those undergoing staging operations compared to those who did not. Overall, 34 patients (10%) recurred, the majority of which were those who had undergone conservative operations (25 of 160 total or 16%). This was the only factor determining recurrence risk including whether or not they underwent a re-staging procedure. Fauvet et al's conclude that little benefit is gained by reoperating on a patient for the purposes of staging unless a patient has a stage IA serous tumor and has undergone cystectomy as a primary operation. However, even in this scenario, no survival benefit is gained by the maneuver and its conduct remains controversial.

COMMENT BY ROBERT L. COLEMAN, MD

The results of this retrospective study of tumors fits nicely into the growing body of literature outlining the natural history of LMP ovarian tumors. Fortunately, long-term survival for women diagnosed with this disease is the rule rather than the exception and outside of those uncommon tumors demonstrating metastatic disease at diagnosis and those with invasive implants, these patients remain predominately relapse-free. As confirmed in this review, those undergoing conservative procedures, that is, in whom ovarian tissue is left behind, are the ones most at risk for relapse. However, the majority of these recurrences are of similar histology and are reliably salvaged with additional surgery to remove the adnexa. Fertility sparing should be considered in those who are interested in childbearing. These findings should be of some comfort to practitioners and patients alike.

However, it is important not to equate these survival characteristics with benignity. For instance, it is remarkable that in the current series more than 58% of the 360 LMP tumors accessioned did not have an intraoperative histological assessment (frozen section). One must remember that patients may not only recur with invasive disease but also can succumb to its benign natural history through indolent and progressive growth. In addition, since re-staging, as defined in this report, is not associated with variable survival dynamics, the procedure may errantly be omitted under the guise that it won't make a difference. While little appears to be gained in those patients with no macroscopic disease by a secondary staging procedure, it shouldn't preclude staging when the diagnosis is suspected intraoperatively.

As has been reported elsewhere as well as in this study, the final and intraoperative histological diagnoses are non-correlative in a significant fraction (> 20%).[1-3] Absence of important intraoperative information makes

subsequent treatment decisions more problematic and may lead to both under- and overtreatment. This was highlighted in a recent review of 2 hospital systems where surgical staging for suspected early ovarian cancer was dichotomized by the presence of a gynecological oncologist. Where staging was not done routinely and treatment decisions were made on the basis of postoperative ovarian histology, approximately 20% more patients were treated than when operative information correctly identified the patients' stage. In addition recurrence rate was reduced from 28% to 10% by correctly identifying true at-risk patients. It is unlikely a similar policy for LMP tumors will have such a dramatic effect but we are nonetheless, left to make the decision to stage or not intraoperatively, and until we can be confident that our final histology will be represented by frozen section we must address the situation conservatively. It is likely we will increase our diagnostic precision for LMP, allowing us to be more selective in whom we stage. Once the diagnosis is confirmed, limited stage patients appear to gain very little from addition surgical evaluation. ■

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Phase II Data on Cetuximab (Erbitux™)

ABSTRACT & COMMENTARY

Synopsis: *In a phase II trial of cetuximab (Erbitux™) given once weekly to patients with advanced colorectal cancer who had failed prior irinotecan treatment, a modest response rate was observed and the toxicity profile was shown to be manageable.*

Source: Saltz LB, et al. *J Clin Oncol.* 2004;22: 1201-1208.

In 2003, colorectal cancer was the fourth most common type of cancer in the United States, and the second leading cause of cancer death.1 The current treatment for metastatic disease consists of the use of chemotherapy with the antineoplastic agents fluorouracil (FU), irinotecan and oxaliplatin. However, once a patient's cancer becomes unresponsive to these agents, there are no effective treatment options. As a result, metastatic colorectal cancer is ultimately fatal and new therapies for this disease are needed. The epidermal growth factor receptor (EGFr) is a transmembrane glycoprotein that is expressed by many tumor types, including colorectal cancer, and is therefore a potential target for anticancer treatment. Upon ligand binding, the intracellular tyrosine kinase is activated, triggering many signaling reactions that control cell growth and survival. Cetuximab is an antibody directed against the ligand-binding domain of the EGFr. Previous studies have demonstrated the ability of this agent block the activation of the EGFr tyrosine kinase by EGF or TGF-a, thereby inhibiting cellular proliferation. Additionally, it has been shown that cetuximab has significantly better activity when administered in conjunction with inactive or minimally active doses of cytotoxic chemotherapy. Saltz and colleagues from the Memorial Sloan-Kettering Cancer Center conducted a Phase II multi site clinical trial with 57 eligible patients. All patients had chemotherapy-refractory colorectal cancer and tumors that expressed EGFr. Additionally, eligible patients had to have previously been treated with and failed irinotecan therapy. All patients were administered cetuximab weekly (400 mg/m^2 the first week, 250 mg/m^2 each additional week) by intravenous infusion for a median of 6.4 weeks (range, 1-67 weeks) and were subsequently analyzed for antitumor activity and drug toxicity.

Five (9%; 95% confidence interval [CI], 3-19%) of the 57 treated patients obtained a partial response and 21 additional patients had either a minor response (tumor reduction between 25% and 49%) or stable disease (either growth or shrinkage of less than 25%). There was no apparent correlation between response and the observed degree of EGFr expression. The most common adverse events were acne-like skin reactions seen in 86% of patients. Of these, 18% (n = 10) were grade 3 but there were no grade 4 reactions observed. There appeared to be a correlation between the presence and severity of the rash and survival. Patients with skin rash of any grade had a superior survival to patients with no skin rash. Other adverse events included asthenia, fatigue, malaise or lethargy (56% with any grade; 18% with grade 3). The median survival from the time of initiation of cetuximab was 6.4 months.

■ COMMENT BY WILLIAM B. ERSHLER, MD

The data presented in this report have supported the advancement of cetuximab to practicing oncologists. The response rates were modest by all accounts, yet, all the patients treated had advanced disease without available

alternative agents with any likelihood of success. It has not been common practice to obtain an analysis of EGFr on colon cancer clinical specimens and it was of interest to note that there was a poor correlation of clinical response to the degree of EGFr expression in this series. Perhaps equivalent response rates will be observed in individuals who do not test positively at all, or other immunohistochemical or molecular techniques will become available that will more precisely predict clinical response.

Where cetuximab will be most effectively used in the treatment of colorectal cancer needs to be clarified. Currently, larger trials incorporating it with chemotherapy as first-line treatment for both the adjuvant setting and for metastatic disease are either underway or in the planning stages. Until such data is available, practicing oncologists may elect to use this new agent in the setting for which it has been FDA approved (ie, for those patients who have progressed on irinotecan therapy). For such patients, with, or without demonstrated EGFr, it would seem that single agent cetuximab offers a better chance for response than any other available agent. ■

References

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High-Dose Imatinib Mesylate (Gleevec®) for CML

ABSTRACT & COMMENTARY

Synopsis: *Imatinib was administered to newly diagnosed patients with chronic-phase myelogenous leukemia at a dose (800 mg daily) double what is commonly prescribed. Cytogenetic and molecular responses were significantly better than observed in an historical cohort of similar patients treated with 400 mg daily. Furthermore, although toxicity was greater, the dose was maintained in nearly two-thirds of the patients. Additional research is needed, but higher-dose imatinib may offer a better chance for long survival and even cure for some patients with this disease.*

Source: Kantarijian H, et al. *Blood*. 2004;103: 2873-2878.

Imatinib mesylate (STI571, Gleevec®) has become the standard first-line treatment for chronic phase chronic myelogenous leukemia (CML). Typically, patients are treated with a dose of 400 mg daily; and prior experience indicates that 95% of such patients experience complete hematological responses and 60-75% are shown to have complete cytogenetic responses.[1,2] However, complete molecular response (undetectable levels of BCR-ABL assessed by polymerase chain reaction) are significantly less common (5-15%). A molecular response has become the goal of therapy inasmuch as such patients have experienced 10-year survival rates of 70-85%.[2-4]

In the current report from M.D. Anderson Cancer Center, 114 patients with newly diagnosed CML were treated with imatinib mesylate 400 mg twice daily. Overall, 109 patients (96%) had a major cytogenetic response (Philadelphia chromosome [Ph] < 35%), and 103 (90%) had a complete cytogenetic response (Ph 0%). With a median follow-up of 15 months, no patient had progressed to accelerated or blastic phase. The estimated 2-year survival rate was 94%. By quantitative polymerase chain reaction (QPCR) studies, 71 (63%) showed BCR-ABL/ABL percentage ratio decreased to less than 0.05%, and 31 (28%) to undetectable levels. Compared with standard-dose imatinib, high-dose imatinib was associated with significantly better complete cytogenetic response ($P = 0.0005$), major molecular response (QPCR < 0.05%; $P = 0.00001$), and complete molecular response (undetectable BCR-ABL; $P = 0.001$).

With regard to adverse effects, high-dose imatinib was associated with more frequent myelosuppression, and for many the doses had to be reduced. Dose reductions were necessitated by myelosuppression in 18 patients (15%, thrombocytopenia in 11, neutropenia in 6, both in 1), skin rash (n = 13, 11%), fatigue (n = 4, 3%), bone pain (n = 7, 6%), fluid retention (n = 5, 4%), congestive heart failure (n = 3), fever or infection (n = 3), liver dysfunction (n = 2), and gastrointestinal (n = 2). Anemia occurred in 40 patients and was treated with erythropoietin. No dose reductions resulted from the occurrence of anemia.

By 3 months of therapy, 68% were receiving the planned dose, whereas the remainder (n = 37) had doses reduced to 600 mg daily (n = 27) or 300 to 400 mg daily (n = 10). The imatinib dose was maintained at 800 mg daily at 6 months in 70 (64%) and in 52 (66%) of 79 evaluable patients at 12 months. Dose reduction to 600 mg daily resolved the toxicity in most patients.

Thus, close to two-thirds of new chronic phase CML patients were able to maintain a dose of imatinib of 800 mg daily, and for the group as a whole, response rates, including molecular responses, were significantly higher than those of a comparable group of 50 patients treated at that institution with a dose of 400 mg daily.

COMMENT BY WILLIAM B. ERSHLER, MD

The treatment of chronic myelogenous leukemia has

evolved dramatically since the introduction of imatinib. With prior therapies, such as busulfan and hydroxyurea, the duration of chronic phase was clearly prolonged but accelerated phase and blast crisis invariably involved in a matter of two to three years. Instituting curative treatment strategies during the chronic phase often involved intensive chemotherapy with allogeneic transplantation, the aggressiveness of which often precluded the major population of those with this disease, patients over the age of 60 years. Even interferon, which clearly enhanced survival, has proven to be a difficult therapy for many patients to tolerate. Imatinib, at 400 mg daily, is clearly well tolerated, even by more frail patients, and has resulted in significantly better response rates and survival. The question raised by the current research is whether higher doses can be sufficiently well tolerated to result in a more effective response, namely a higher rate of molecular remissions. The data presented are intriguing, but must be considered preliminary. Before practicing oncologists adopt the higher dose regimen as the standard approach a larger, prospective trial must be undertaken. One such trial might include a randomization to either standard dose (400 mg daily) to high dose (800 mg daily) with a third arm receiving interferon. ■

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BRCA Germline Mutations in Jewish Women with Uterine Serous Papillary Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *The loss of heterozygosity in the tumor tissue of carriers coupled with the high frequency of patient and family history of breast and ovarian malignancies suggest that USPC might be part of the manifestation of familial breast-ovarian cancer in Ashkenazi Jews.*

Source: Lavie O, et al. *Gynecol Oncol*. 2004;92: 521-524.

Lavie and colleagues previously described a possible link between germline mutation in the BRCA genes and the occurrence of the uncommon, but aggressive uterine papillary serous carcinoma (UPSC). The purpose of the current study was to expand the investigation, evaluate the incidence of personal breast cancer and family history and to determine if tumor tissues harbored similar genetic mutations as the germline. To do this, they retrospectively identified 27 women consecutively diagnosed with UPSC over a 2½ year interval at 3 institutions. Identified cases were interviewed for family history and given genetic counseling. Peripheral blood was taken for genomic DNA analysis and paraffin-embedded tissue was harvested for loss of heterozygosity analysis (LOH). Mutational analysis was conducted for one of the 3 well-characterized founder mutations for women of Ashkenazi decent. Overall, 4 of 20 (20%) Ashkenazi and 0 of 7 non-Ashkenazi women were identified with a founder mutation. Personal history of breast cancer was identified in 7 (35%). Family history of breast (65%), and ovarian (20%) cancer were common. The diagnosis of breast cancer preceded uterine cancer by 11.5 years. LOH analysis identified loss of the wild-type allele in 3 of the 4 BRCA1 mutations. Lavie et al concluded that Ashkenazi women diagnosed with UPSC have a high incidence of BRCA founder mutations. LOH analysis coupled with the significant family history reported in this cohort suggested that UPSC might be a clinical manifestation of the familial breast-ovarian cancer syndrome in Ashkenazi women.

■ COMMENT BY ROBERT L. COLEMAN, MD

There is little underestimation of the clinical significance conveyed in identifying a familial cancer syndrome for a particular patient. Once hidden from public record for fear of "genetic discrimination," the knowledge of an inherited predisposition has allowed physicians and patients to not only critically assess cancer risk but also evaluate potential preventive strategies that could impact that risk over time. As more sophisticated models assessing risk are developed and acceptance for available testing is increased, greater precision in counseling can be realized. A necessary component of this counseling is understanding how to interpret risk estimates and where this risk may manifest.

As obstetrician/gynecologists, our closest clinical experience in this regard comes in the care of women with mutation in the BRCA family of genes. The familial breast-ovarian cancer syndrome, most commonly characterized by an increase in lifetime risk of both breast and ovarian cancer, is infrequently diagnosed (about 10% of primary ovarian cancers), yet it is the subject of intense investigation. Important information from this work has identified, for instance, that a wide

range of variable penetrance exists between different families; specific cohorts are at risk because of their ethnicity (Ashkenazi Jews); and intervention strategies such as oral contraceptives and prophylactic surgery (salpingoophorectomy, mastectomy) appear to reduce the risk of cancer at both sites. New developments continually shape our understanding of the disease process and with this knowledge, new recommendations.

Lavie et al raise another consideration in the current article. They reasoned that since UPSC and serous epithelial ovarian cancer have similar morphology and clinical behavior and since ovarian cancer in Ashkenazi Jewish women is associated with the high background incidence of BRCA founder mutations, there might be an association between UPSC occurrence and BRCA mutation. Although only 4 women with mutations were identified in the cohort of Israeli Ashkenazi Jews, the 20% incidence is dramatically different than the Ashkenazi population risk in general (2%) and surprising similar to the incidence of mutation in their women diagnosed with either ovarian (30%) or breast (10%) cancer. Loss of heterozygosity analysis suggests the germline mutation was potentially causally related to their cancer occurrence. The clinical implication of documenting UPSC as a potential clinical manifestation of the cancer syndrome lies in screening and prophylactic surgery. That is, if the disease is a future risk for women identified with or at risk for mutation of BRCA, should our recommendation for risk reduction include hysterectomy?

To answer this question appropriately, more clinical data are needed. The association documented in the current report is far from congruent with other investigations. For instance, in the largest series of UPSC patients for whom BRCA analysis was conducted, no BRCA1 or BRCA2 mutations were found; in a smaller series of UPSC tumors by Goldman et al, 3 of 9 cases were identified with BRCA2 mutations, whereas in the current report, only mutations in BRCA1 were found. Nonetheless, management of women undergoing prophylactic surgery for known or suspected BRCA mutation is more complex when uterus is left *in situ*. It has been documented that along with ovarian cancer, the relative risk for tubal malignancy is significantly elevated. Although most tubal cancers are distally situated, removal of the entire tubal segment cannot be completely accomplished by salpingoophorectomy—a theoretical consideration. In addition, newly castrated young women will likely choose hormone therapy for symptomatic indications. Generally, this medication is prescribed as a combination in those with a uterus to offset the risk for endometrial cancer. However, the associated risks for subsequent breast cancer with combination hormone replacement therapy have been suggested in recent reports from the Women's Health Initiative trials. Future reports from the estrogen-alone cohort in particular regard to breast cancer risk are awaited. If a modulated risk is seen in this latter cohort, the advocacy for hysterectomy may gain support, albeit recognizably, a more invasive procedure.

Nonetheless, if clear association of UPSC as a clinical manifestation of the familial syndrome can be made, it should prompt us to expand our discussions with these high-risk women and potentially modify our recommendations for prophylactic surgery. At the end of the day, provocative data, as that raised by Lavie et al, need to be critically evaluated. The recommendation for universal hysterectomy in affected patients wanting prophylactic surgery is premature. Data from additional analytical trials will help to further refine this recommendation, hopefully, improving the lives of women identified with familial cancer risk. ■

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Suggested Reading

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- Grann VR, et al. *J Clin Oncol*. 2002;20:2520-2529.
- Rossouw JE, et al. *JAMA*. 2002;288:321-333.
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CME Questions

15. After adjuvant chemotherapy for stage II or III colorectal cancer, for those who develop recurrent disease, the greatest likelihood of having potentially resectable metastatic lesions was demonstrated to be:

a. for those in whom disease recurrence was discovered by the development of symptoms.
b. for those in whom disease recurrence was discovered by rising CEA titer.
c. for those in whom disease recurrence was discovered by CT scan.
d. for those in whom disease recurrence was discovered by routine colonoscopy.

16. **Cetuximab (Erbitux™) was demonstrated in phase II trial in patients with advanced colorectal cancer refractory to irinotecan, to produce objective, measurable response in approximately what percent of patients?**
    a. 0%
    b. 10%
    c. 45%
    d. 75%

17. **Compared with an imatinib dose of 400 mg daily, a dose of 800 mg daily for patients with chronic phase CML was found, in the research by Kantarijian and colleagues, to result in each, except which of the following?**
    a. A higher level of marrow toxicity
    b. A greater cytogenetic response rate
    c. A greater molecular response rate
    d. A higher survival rate

Answers: 15 (c); 16 (b); 17 (d)

In Future Issues:

Running the Gamut on Treatment for Follicular NHL

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Migraine and Subclinical Brain Lesions

Source: Kruit MC, et al. *JAMA*. 2004;291:427-434.

The data on the relationship between migraine and other vascular events such as stroke have been conflicting, although in some populations (such as young women smokers who suffer migraine with aura) the adverse association is more clear-cut. Because such a high proportion of women, and a not-insubstantial population of men suffer migraine, any important association with other major morbidities becomes epidemiologically compelling.

Using MRI scans in a population of migraine sufferers without history of prior stroke or TIA, infarcts and white matter lesions were defined, all by the same neuroradiologist who was blinded to the clinical data about the patients (n = 435, inclusive of 140 controls). Most patients (71%) were female, the mean age was 48 years, and patients were equally divided between migraine with and without aura.

Although the absolute number of infarcts demonstrated only a trend towards being more frequent in migraneurs, it was the posterior circulation infarcts which were markedly more common (7-fold increase in migraine population vs controls), an effect which was even more exaggerated in the migraine with aura category (odds ratio = 13.7). In the total unselected population, no difference in white matter lesions between migraine sufferers and controls was discerned; however women migraneurs had an increased odds ratio (OR = 2.1) for white matter lesions compared to controls.

None of these patients had any prior evidence of cerebral ischemic events. The relationship between migraine and increased risk of cerebral ischemia prompts consideration of whether more vigorous prevention of migraine might reduce risk of subsequent tissue damage. ■

Memantine Treatment in Alzheimer Disease

Source: Tariot PN, et al. *JAMA*. 2004;291:317-324.

Memantine (MEM) is the first clinically available NMDA receptor antagonist with demonstrated clinical efficacy and an acceptable adverse event profile for persons with Alzheimer disease (ALZ). Cholinesterase inhibitors like donepezil (DON) might work in a complementary fashion, hence this MEM + DON trial.

Subjects with ALZ (n = 404) who had been on a stable dose of DON for at least 6 months, and were free of known secondary etiologies for dementia, were randomized in a double-blind fashion to MEM titrated from 5 mg/d up to 20 mg/d (administered as 10 mg b.i.d.) for 6 months, vs placebo. DON was continued in both the placebo and the MEM treatment arm.

Changes in cognitive function, functional capacity, and global outcome were measured throughout the trial, the primary outcome being based upon scores on the Severe Impairment Battery and Activities of Daily Living Inventory.

There was a statistically significant positive effect of MEM when added to DON, complemented with a very favorable adverse effect profile: more patients in the placebo group withdrew due to adverse events than in the MEM group. Only headache and confusion were more common in the MEM group, both of which occurred in less than 10% of recipients. In addition to being useful as ALZ monotherapy, there may be additional clinical benefits from combining MEM with DON in ALZ therapy. ■

Casual Postprandial Glucose Levels in Type 2 Diabetes Management

Source: El-Kebbi IM, et al. *Diabetes Care*. 2004;27:335-339.

Tight control of type 2 diabetes (DM2) has been proven to reduce microvascular complications. Use of the hemoglobin A1c to assess long-term control is standard, but for modulation of treatment, timed specimens (eg, fasting, 1-2 hours postprandial) obtained by patient self-monitoring of blood glucose are often the information clinicians use to make choices about therapy modification.

Unless instructed otherwise, most DM2 patients are 1-4 hours postprandial at the time of an office visit. El-Kebbi, et al, investigated whether casual glucose levels obtained at the office visit might function as an adequate barometer of glucose control to

help modify treatment.

Established DM2 patients (n = 1827) at the Grady Diabetes Clinic (Atlanta) underwent simultaneous A1c and casual glucose measurement during their regular visit. The correlation between casual glucose measurement and A1c was strong (correlation coefficient = 0.63). The presence of a casual glucose > 150 predicted an A1c > 7.0 with a sensitivity of 78% (positive predictive value = 80%).

El-Kebbi and colleagues suggest that a casual plasma glucose greater than 150 mg/dL may serve as a surrogate for A1c; results above this level should prompt an intensification of therapy. ■

Exemestane after Tamoxifen Therapy in Breast Cancer

Source: Coombes RC, et al. *N Engl J Med*. 2004;350(11):1081-1092.

Tamoxifen (TAM) is well established to reduce, over 5 years, both risk of breast cancer (BCA) recurrence (47%) and mortality (26%) among women who have undergone surgery for BCA and who have estrogen-receptor positive tumors. Exemestane (EXE) is classified as an irreversible steroidal inactivator, and works by blocking the enzyme (aromatase) which is responsible for converting androgens to estrogens, ultimately inhibiting aromatization by about 98%. Although TAM is of remarkable positive benefit, it is not without risks, including increased likelihood of endometrial cancer attributed to endometrial stimulation. EXE is not known to induce endometrial proliferation, or increase proclivity for endometrial cancer.

The Intergroup Exemestane Study (IES) investigated whether substituting EXE for TAM after 2-3 years would provide better outcomes than simply treating with TAM continuously for 5 years. Study subjects were postmenopausal women (n = 4742) who remained free of recurrence during sustained TAM treatment. EXE (25 mg p.o. q.d.) was substituted for TAM in one half of the subjects.

After a median followup of 30.6 months, the risk of recurrence, contralateral BCA, or death was reduced by 32% in the EXE group compared with TAM. The adverse effects seen more frequently with EXE than TAM included diarrhea and arthralgia, but thromboembolisms was almost twice as common in the TAM group. Coombes and colleagues suggest that switching women from TAM to EXE at the 2-3 year point in treatment may provide more favorable outcomes. ■

An Analysis of How Long Patients Remain on Various Antihypertensive Therapies

Source: Esposti LD, et al. *J Clin Hypertens*. 2004;6:76-84.

The term 'drug efficacy' is technically intended to reflect impact of an agent on a designated end point in a study population participating in a clinical trial. 'Drug effectiveness,' on the other hand, refers to the 'real life' effects drug treatment produces as seen separately from a clinical trial; ie, what impact might be seen when 'typical patients' use a medication in, for instance, the community setting.

As many as half of patients who begin antihypertensive drug therapy (HTN-Rx) discontinue treatment within a few months of initiation. Study subjects from the area in and around Ravenna, Italy comprised this hypertensive patient population (n = 14,062). All were first time recipients of a new HTN-Rx. 'Persistent patients' were defined as either maintaining, combining with, or switching from their initial HTN-Rx to another HTN-Rx, for a duration of > 273 days from the day of enrollment.

Discouragingly, 48% of patients discontinued treatment after a single prescription! Medication choices were similar to those commonly used in the United States (ACE/ARB/HCTZ/CCB/Beta Blocker). Angiotensin Receptor Blockers demonstrated the highest continuation rate, followed by ACE inhibitors, CCBs, and Diuretics.

Cost of treatment decreased as age increased, and increased for persons who switched or combined agents. Angiotensin receptor blockers were the most expensive single agents. Overall, specific individual drug cost and pattern of drug persistence correlated best with total cost for hypertension treatment. These data suggest that although drug cost is important, aspects of the drug treatment which affect persistence patterns ultimately have a substantial effect on overall cost. ■

Association of Endothelial Dysfunction with Insulin Resistance and Carotid Wall Thickening in Hypertension

Source: Suzuki M, et al. *Am J Hypertens*. 2004;17:228-232.

Endothelial dysfunction (END) is a fundamental defect in essential hypertension (HTN) and is closely associated with carotid wall thickening (CWT), a consistent marker for early atherosclerotic change. Insulin resistance (IR) is also associated with both HTN and CWT, suggesting a potential relationship between IR and END.

HTN subjects (n = 41) were studied if they met inclusion criteria including HTN, no diabetes, no suggestion of secondary HTN, no major cardiovascular, renal, hepatic, or other endocrine disease, no smoking, and no medications which modulate carbohydrate or lipid metabolism (eg, statin, steroids) for at least 12 months. All subjects underwent measurement of endothelial function, carotid interomedial thickness by ultrasound, and insulin sensitivity as defined by insulin/glucose infusion.

END was found to be associated both with IR and CWT. The changes in CWT and END were strongly associated, suggesting a close correlation between functional (END) and structural (CWT) atherosclerotic changes. The confirmed association between END, CWT, and IR may prompt consideration of investigation to seek causality between, eg, IR and CWT ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Atherosclerosis Reversed With Lipid-Lowering Drugs

When it comes to treating lipids in patients with heart disease, the mantra may be, "The lower the LDL, the better." Data from the multicenter Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial indicate that aggressive reduction of atherogenic lipoproteins prevents progression of disease. The study randomized 654 patients with coronary disease to pravastatin 40 mg/d (moderate lipid-lowering regimen) or atorvastatin 80 mg/d (intensive lipid-lowering regimen). After 18 months of therapy, 502 patients were evaluable with baseline and post-treatment intravascular ultrasounds. The primary outcome was percentage change in atheroma volume. Intensive lipid-lowering therapy with atorvastatin resulted in a decrease of LDL cholesterol from an average of 150 mg/dL to 79 mg/dL, while pravastatin therapy resulted in a decrease to 110 mg/dL. C-reactive protein decreased 36.4% with atorvastatin and 5.2% with pravastatin ($P < .001$). Progression of coronary atherosclerosis did not occur in the atorvastatin group, while coronary atherosclerosis progression did occur in the pravastatin group compared with baseline. The authors suggest that the data support aggressive lipid lowering, below the current national guidelines for secondary prevention in patients with coronary atherosclerosis (*JAMA*. 2004;291:1071-1080). It is of note that this study employed the relatively new technology of coronary ultrasound, which more effectively measures plaque volume as opposed to coronary angiography, which merely quantifies the lumen. Still, this technology is relatively new, as pointed out in an accompanying editorial, but the results appear to be valid. The editorial also points out that the moderate lipid-lowering regimen in the study did not achieve levels of LDL lowering recommended by national guidelines, which suggest lowering LDL below 100 mg/dL for secondary prevention. The authors recommend focus on all risk factors in patients with coronary disease, including LDL lowering at least to levels recommended in national guidelines (*JAMA*. 2004;291:1132-1134).

Positive Alendronate Data in Osteoporosis

Does alendronate prevent fractures after 10 years of therapy? According to a new multicenter placebo-controlled trial, the drug is effective and safe over 10 years in women with osteoporosis. Data from the study are from a follow-up of 2 identical 3-year trials of alendronate therapy followed for an additional 7 years. In this follow-up study, women were randomized to 3 daily doses of alendronate or placebo. The 3 active treatment groups included women who took alendronate 5 mg or 10 mg daily for the entire 10-year study. A third group took 20 mg of

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alendronate daily for 2 years and 5 mg daily in years 3, 4, and 5 followed by 5 years of placebo. This last group was called the "discontinuation group." Women in the original placebo group ended up receiving alendronate in years 4 and 5 and then were discharged. There were 247 women who participated in all 4 phases of the study. Treatment with 10 mg of alendronate daily for 10 years resulted in statistically significant increases in bone mineral density at the following sites: 13.7% increase, lumbar spine; 10.3%, trochanter; 5.4%, femoral neck; and 6.7%, proximal femur as compared with baseline values ($P < .001$; 95% CI for all groups). The percentage increases for the 5 mg group were 9.3%, lumbar spine; 4.8%, trochanter; 2.8%, femoral neck; and 2.9%, proximal femur. Alendronate also resulted in fewer fractures and lower rates of loss of stature over the 10-year period. Discontinuation of alendronate resulted in a gradual loss of bone density. The authors conclude that continued treatment with 10 mg of alendronate daily for 10 years was associated with a sustained therapeutic effect on bone density and bone remodeling. Concern over increase fracture rates with bisphosphonates over time was not validated by the study (*N Engl J Med*. 2004;350:1189-1199).

NSAIDs For Myocardial Infarction

Nonaspirin NSAIDs, especially ibuprofen and naproxen, may protect against myocardial infarction in patients who are not taking aspirin. Researchers from Pennsylvania conducted a case-control study with cases of first, nonfatal MI identified prospectively with random controls from the community. The use of a nonaspirin NSAID was associated with a significant reduction in MI compared to those not using aspirin (OR 0.53; 95% CI). The adjusted odds ratio for ibuprofen was 0.52 and for naproxen was 0.48. The odds ratio for aspirin alone in this study was 0.79. The combination of aspirin with a nonaspirin NSAID trended toward increased risk of MI and worsened as the frequency of nonaspirin NSAIDs use increased; however, the confidence intervals for this determination were very wide. The authors conclude that in patients who are not taking aspirin, a nonaspirin NSAID is associated with a reduced risk of MI. The concomitant use of aspirin for cardioprotection along with a nonaspirin NSAID needs further study (*J Am Coll Card*. 2004;43:985-993).

Four-Hour Window for CAP Patients

Medicare patients with community-acquired pneumonia (CAP) fare better if they receive their first dose of antibiotics within 4 hours of hospitalization, according to new study. The records of nearly 14,000 Medicare patients admitted for CAP, who had not received antibiotics as outpatients, were reviewed. The administration of an antibiotic within 4 hours of arrival to the hospital was associated with reduced in-hospital mortality (6.8% vs 7.4%; adjusted odds ratio [AOR] 0.85; 95% CI, 0.74-0.98), reduced mortality within 30 days of admission (11.6% vs 12.7%; AOR 0.85; 95% CI, 0.76-0.95), and reduced length of stay as measured by hospitalization exceeding the 5-day median (42.1% vs 45.1%; AOR 0.90; 95% CI, 0.83-0.96). Early administration of antibiotics also resulted in a 0.4-day shorter length of stay. The study did show that the majority of patients (60.9%) received antibiotics within 4 hours of arrival (*Arch Int Med*. 2004;164:637-644). Current CAP guidelines generally recommend initiation of an antibiotic within 8 hours of arrival, but this study suggests that those guidelines may not be aggressive enough.

FDA Actions

Rofecoxib (Vioxx) has been approved for the treatment of migraine attacks with or without aura in adults. The approval was based on a large study that showed that the single dose of rofecoxib, either 25 or 50 mg, effectively reduced migraine pain at 2 hours and reduced the use of rescue medications.

The FDA has issued a Public Health Advisory about the need for physicians, patients, and families to closely monitor adults and children with depression when beginning treatment certain antidepressants and has asked the manufacturers of these drugs to include new warnings in their labeling about the potential for increased suicidality. The antidepressant drugs are the serotonin reuptake inhibitors fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro); and the non-SSRI antidepressants bupropion (Wellbutrin), venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron). ■