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INSIDE

One-Stage Surgery for Patients with Colorectal Cancer Presenting with Liver Metastases

ABSTRACT & COMMENTARY

Synopsis: *Approximately 20% of patients with colorectal cancer will have hepatic metastases at the time of original presentation. Partial hepatectomy has become increasingly used in the treatment of liver metastases, but the timing of this procedure for those who present with liver involvement remains an unsettled question. The current single-institution experience would suggest that for selected patients, a simultaneous, one-stage procedure offers a safe and effective treatment strategy.*

Source: Tanaka K, et al. *Surgery*. 2004;136:650-659.

There has been increasing enthusiasm for a surgical approach to hepatic metastases from colorectal primary cancers. However, consensus has not been reached concerning the timing of hepatectomy in patients who at initial presentation are found to have liver involvement. Tanaka and colleagues from Yokohama City University Graduate School of Medicine retrospectively obtained data for 39 consecutive patients with synchronous colorectal cancer hepatic metastases who underwent curative-intent, simultaneous (one-stage) hepatectomy and resection of the colorectal primary. These patients were among 91 who presented to their institution with hepatic metastases and primary colorectal cancer during a 12-year period (1992-2003). Simultaneous resections were performed in those (of the 91) with a relatively small number of liver neoplasms considered to be completely removed by a relatively simple hepatectomy procedure, and were made on a patient-by-patient basis. Liver resection was considered contraindicated at the time of primary operation in 50 patients for the following reasons: poor performance status (4 patients), massive neoplasm (2 patients), unfavorably located neoplasm (2 patients), multicentricity (6 patients) and multiple, bilobar liver metastases (36 patients). Of the 41 who underwent simultaneous resection, 2 were excluded from analysis because of concomitant extrahepatic metastases, which could not be resected completely.

The data on the 39 patients who underwent simultaneous prima-

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ry and hepatic metastases resection with curative intention were reviewed using both univariate and multivariate analyses with regard to success and safety outcomes.

Regarding safety, no patient died within 60 days of the operation. However, 11 patients (28%) had postoperative complications. Of several clinicopathologic factors, including age, primary site, TNM stage, histology of primary neoplasm, extent and number of liver nodules, maximum liver neoplasm size, resected liver volume, hepatectomy procedure used, duration of operation and intraoperative blood loss, only resected liver volume was significantly different between the groups with or without complications. The mean liver volume removed from those that were to develop postoperative complications was 350 grams (range, 80-870 grams) compared to 150g (range, 20-370 grams) from those that did not develop complications ($P < .05$).

Overall survival at 1, 3, and 5 years after simultaneous resection of colorectal cancer and hepatic metastases were 86%, 68% and 53% respectively. During follow-up, 28 patients (72%) developed recurrence (liver only, 16; liver plus extrahepatic, 4; extrahepatic only, 8). Disease-free survival rates at 1, 3, and 5 years were 64%, 20%, and 16%, respectively.

By univariate analysis, a number of potential variables on survival were examined, but only histological features of the primary neoplasm ($P < 0.01$) and age ($P < 0.05$) were identified as significant prognostic determinants. Survival was better in patients with well-to-moderately differentiated primary adenocarcinoma, and in younger patients (younger than 70 years of age). To identify independent prognostic determinants multivariate regression analysis using a proportional hazard method involving a Cox model was performed. This analysis indicated that the only independent factor adversely affecting survival was the histology of the primary neoplasm (specifically, poorly differentiated adenocarcinoma or mucinous carcinoma vs other types).

COMMENT BY WILLIAM B. ERSHLER, MD

Hepatic metastases are found in 15%-20% of patients undergoing an operation for colorectal cancer.[1] New and more precise imaging techniques coupled with methods of hepatectomy have improved the outlook for patients with metastatic disease. Although there may be theoretical reasons for waiting and possibly performing two procedures for patients who present with metastatic disease, simultaneous resection would clearly be preferable from a patient's perspective if safety and outcome data were comparable. Some researchers[2,3] believe that the survival benefit from hepatic resection is determined by biological features of the neoplasm, rather than by early detection. Particularly for synchronous hepatic metastases, several investigators[2-4] have recommended interval (ie, delayed) hepatic resection to assess the biological behavior of the metastatic disease. Scheele et al[3] demonstrated poor prognosis in patients with synchronous metastases, attributing some of the poor outcome to failure to resect micrometastatic hepatic lesions in patients who underwent resection of the overt liver metastases as part of the primary procedure. This and similar reports have led to a policy in which resection of the primary neoplasm and of liver tissue known to contain metastases are to be separated by 3 to 6 months. Theoretically this period of time would allow those occult micrometastases to become evident. However, other surgical teams have demonstrated no decrement in 5-year survival when patients underwent a one-stage combined procedure.[5,6]

The current report adds useful perspective to this dialogue. It would seem that the outcome for selected

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EDITORIAL GROUP HEAD: Lee Landenberger.
MARKETING PRODUCT MANAGER: Schandale Komegay.
MANAGING EDITOR: Robert Kimball.
ASSOCIATE MANAGING EDITOR: Leslie Hamlin.

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Editorial E-Mail Address:
robert.kimball@thomson.com

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patients may be at least as good with simultaneous resection of primary and hepatic lesions. Included would be those younger patients with more favorable histology and whose involvement in the liver would require a relatively small resection. These criteria, however, would restrict simultaneous resection to less than 50% of patients who present initially with liver metastases.

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Efficacy of 5-Fluorouracil-Based Chemotherapy in Elderly Patients with Metastatic Colorectal Cancer: A Pooled Analysis of Clinical Trials

ABSTRACT & COMMENTARY

Synopsis: *Fit elderly patients benefit at least to the same extent from palliative chemotherapy with 5-FU as younger patients. Infusional 5-FU was shown to be more effective than bolus 5-FU in both age groups. Therefore, standardized palliative chemotherapy should generally be offered to elderly patients and they should not be excluded from clinical trials.*

Source: Folprecht G, et al. *Ann Oncol*. 2004;15: 1330-1338.

Malignancies form the second most common cause of death after cardiovascular diseases in the 70 years and older age group. In this age group, colorectal cancer is the second most common cause of cancer death. Systemic chemotherapy is the treatment of choice for patients with metastatic colorectal cancer to prolong survival, and to improve symptoms and quality of life.

5-Fluorouracil (5-FU)-based treatment is generally offered to patients and has been the standard of care for decades. Biochemical modulation of 5-FU and/or administration as a continuous infusion have resulted in increased response rates and prolonged progression-free survival, while the influence on overall survival has been limited. There is still uncertainty regarding to what extent systemic palliative chemotherapy should be offered to elderly patients with colorectal cancer. This fact is related to the unfortunate underrepresentation or even exclusion of elderly patients from clinical trials and also to the total lack of studies in unfit elderly patients.[1]

Increased attention has recently been paid to the management and outcome of elderly patients with colorectal cancer. Population-based series focusing on surgery and adjuvant therapy have confirmed that older patients are more often inadequately staged and fewer elective operations are performed, and that they are less likely to receive adjuvant chemotherapy and/or radiotherapy. In contrast to these facts, a recently published meta-analysis and population based analyses showed that elderly patients with colon or rectum cancer benefit from adjuvant chemotherapy or radiochemotherapy to the same extent as younger patients.[2-4] The reason why elderly patients are less likely to be offered adequate diagnostic procedures or treatment for their tumor is multifactorial. Advanced age is often associated with increased health problems such as declining organ functions, decreasing cognitive or socio-economic abilities and additional diseases. Although co-morbid conditions are associated with a higher operative morbidity and mortality, improvements in supportive means for anesthesia and post-operative management have reduced the mortality associated with surgical procedures.

This may also be important for patients with metastatic colorectal cancer as reports are emerging on secondary resectability of metastasis following more intensive systemic chemotherapy. To further expand the knowledge base, Folprecht and colleagues undertook a retrospective analysis using original data from 22 phase II and phase III trials conducted throughout Europe and identified a total of 629 patients older than 70 years of age which represents, to our knowledge, the largest cohort that has been analyzed to date.

COMMENT BY STUART M. LICHTMAN, MD

This paper analyzes data from 19 randomized and 3 phase II trials in metastatic colorectal cancer. The regimens were classified as 5-FU treatment given as a bolus or as infusional regimen. A total of 629 patients older than 70 years of age were identified which represented 16.4% of the total study population. Four hundred and eighty-four patients belonged to the age group 70-75 years (12.7% of the study population), 125 to the age

group 75-79 years (3.3%) and 20 to the age group older than 80 years (< 1%). Approximately 84% of patients were older than 70 years of age, which was quite consistent over all study groups from European countries, with the exception of 2 trials. Objective tumor response was observed in 22% of the whole population. Patients in the older age group (older than 70 years) had the same chance of response to fluoropyrimidine-based treatment as younger patients (24% and 21%; $P = 0.14$). Patients older than 70 years of age had a median PFS of 5.5 months, which was similar to younger patients at 5.3 months. Overall survival in elderly patients of 10.8 months was not significantly different to that of younger patients who had a median OS of 11.3 months. There was no trend in PFS, OS or response rate between the age groups 70-74, 75-79 and older than 80 years. Comparing bolus and infusional 5-FU administration schedules, overall survival was significantly longer in patients receiving infusional 5-FU (12.3 vs 10.7 months; $P < 0.0001$). PFS was also significantly longer in both age groups.

Response rates were increased in patients treated with infusional 5-FU. In patients younger than 70 years receiving infusional therapy, a 7.7% difference in overall response was seen compared with younger patients treated with bolus therapy. Patients older than 70 years had a 9.9% higher overall response with infusion than bolus (31.2% vs 21.3%; $P = 0.014$).

This analysis and other studies clearly show that elderly patients who are eligible for clinical trials derive the same benefit from therapy. These studies usually exclude patients with significant comorbidity and functional impairment. There fore they often not representative of the elderly population as a whole. The decision making process has become more complex with the availability of irinotecan, oxaliplatin and capecitabine. The infusional 5-FU regimens, or those using capecitabine, with either oxaliplatin or irinotecan should be offered to older patients with adequate performance and functional status.[6-8] Most of these patients can also tolerate the addition of bevacizumab to these regimens.[9,10] Care must be taken in older patients with significant cardiovascular disease. Single agent regimens with 5-FU or capecitabine can be offered to those with significant comorbidity.[11] Cetuximab either a single agent or with intravenous therapy can also be an acceptable palliative regimen.[12-14] Folprecht et al recommend designing specific clinical trials that include unfit elderly patients, with reduced general condition and more co-morbidities, especially as these unfit patients seem to represent the majority of elderly patients and no valid data are available from this large subgroup of patients suffering from metastatic colorectal cancer. ■

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Breast Density and Recurrent Disease

ABSTRACT & COMMENTARY

Synopsis: *Breast tissue density, as determined by mammography, is known to be a risk factor for the development of invasive breast cancer. In the current analysis of a subgroup of patients participating in the NSABP B-17 trial, those women with highly dense breast tissue were found to have significantly more subsequent breast cancer. Thus, a quantitative assessment of breast density may prove useful in assessment of additional breast cancer risk for patients having breast-conserving surgery for DCIS.*

Source: Habel LA, et al. *J Natl Cancer Inst*. 2004;96: 1467-1472.

Among risk factors, mammographic density, or the extent of the breast occupied by radiologically-dense tissue remains a powerful predictor of subsequent disease. The appearance of breast tissue on mammogram is determined by the relative components of fat, connective tissue and epithelial tissue. Connective and epithelial tissue are more highly dense, whereas fat is translucent by this technique. Women with extensive areas of mammographic density have been found to be at increased risk of developing breast cancer.[1]

Women diagnosed with ductal carcinoma in situ (DCIS) and treated with breast conserving surgery are

at an increased risk of developing invasive breast cancer in the ipsilateral breast, and to a lesser extent in the contralateral breast as well.[2-3]

Although numerous studies have examined the association between mammographic density and risk of primary breast cancer, this feature has not been previously investigated with regard to the prediction of subsequent breast cancer after either invasive breast cancer or DCIS. Habel and colleagues examined the data from 504 women participants of the National Surgical Adjuvant Breast and Bowel Project B-17. In this subgroup of patients approximately 6.6% had breasts categorized as highly dense (ie, > 75% of the breast occupied by dense tissue). After adjusting for treatment with radiotherapy, age, and body mass index, women with highly dense breasts had 2.8 (95% confidence interval [CI] = 1.3-6.1) times the risk of subsequent breast cancer (DCIS or invasive), 3.2 (95% CI = 1.2-8.5) times the risk of invasive breast cancer, and 3.0 (95% CI = 1.2-7.5) times the risk of any ipsilateral breast cancer, compared with women with less than 25% of the breast occupied by dense tissue.

These findings suggest that the risk of second breast cancers may be increased among DCIS patients with highly dense breasts. An assessment of mammographic density, and a reporting of such findings in quantitative terms may prove to be useful in assessing patient risk for subsequent invasive cancer and in investigating prevention strategies.

COMMENT BY WILLIAM B. ERSHLER, MD

Dense breast tissue is relatively more glandular (less fat) and therefore more likely to harbor malignant disease. Women with DCIS treated with breast conserving surgery are at substantially increased risk of subsequent cancer in the involved (ipsilateral) breast, and to a lesser extent, in the unaffected (contralateral) breast.[2,3] This may be because of residual microscopic disease after surgery. To the extent that dense breast tissue is a reflection of a hormonal environment supportive of active breast proliferation, recurrence rates might be expected to be higher with increasing breast density. Furthermore, because mammograms are more difficult to assess in women with dense breasts, the extent of a DCIS tumor may be more difficult to determine allowing for the chance for incomplete excision. Furthermore, it is possible that disease surveillance (eg, mammography, clinical breast examination) after treatment for the primary DCIS tumor is less accurate among women with highly dense breasts.

In the current series, most of the patients were 50 years of age or older and approximately 6.6% had breasts categorized as highly dense. As expected, percent density decreased with increasing age and with body mass index (BMI). Density was not significantly associated with treatment-related factors (ie, radiotherapy, status of surgical margins). Of the 504 eligible women on this trial, mammograms of sufficient quality were available on 392, and these patients served as the analysis cohort. Of these, 130 had a subsequent breast cancer event; 91 cases in the ipsilateral breast, 28 in the contralateral breast and 11 with regional (nodal) or distant metastases. As was true for the entire B-17 study population,[4,5] risk of subsequent ipsilateral breast cancer was independently associated with radiotherapy, comedo necrosis, and appearance of micro calcifications. In addition, risk of subsequent breast cancer was independently associated with age, menopausal status and BMI. Although qualitative measures of breast density was not associated with increased risk, quantitative assessment as performed in this cohort, was highly predictive of subsequent breast cancer event. Of note, however, the risk of subsequent breast cancer was not markedly different for women in the lower three categories of percent density and there was no statistical evidence of a linear increasing trend across ordinal categories of density. Of note, relative risks for developing breast cancer remained even when the follow-up period was initiated 2 or more years after DCIS diagnosis.

Thus, there is now reasonable evidence that the risk of subsequent breast cancer is increased among DCIS patients with highly dense breasts and that this association did not appear to be limited to certain time periods after DCIS diagnosis. Mammographic density assessment at diagnosis may aid in risk assessment for women with DCIS, although larger studies will be needed to confirm this finding. Furthermore, a standardized method of assessing and reporting mammography determined breast density will need to be developed before clinicians will be able to incorporate this finding into the prescription of a prevention strategy for individual patients. ■

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Gemcitabine, Dexamethasone and Cisplatin Prove Effective for Recurrent Diffuse Non-Hodgkin's Lymphoma

ABSTRACT & COMMENTARY

Synopsis: *Standard treatment for recurrent, diffuse non-Hodgkin's lymphoma remains to be established, but several studies have indicated that autologous stem cell transplant has resulted in improved survival. For those with bulky recurrence, pre-transplant, second-line chemotherapy is recommended. In this setting, an optimal regimen would not commonly produce severe marrow toxicity as mobilization of stem cells will be required for optimal reconstitution after transplant. In the current trial, gemcitabine, dexamethasone and cisplatin (GDP) administered in 21-day cycles resulted in an overall response rate (after 2 cycles) of 49%. Furthermore, after 2 cycles, stem cell mobilization was successful in 22 of 23 patients for whom such an approach was considered appropriate. Thus, GDP is an effective salvage regimen for recurrent large cell lymphoma, particularly in the pre-autologous stem cell transplant setting.*

Source: Crump M, et al. *Cancer*. 2004;101(8): 1835-1842.

For patients with relapsed, aggressive non-Hodgkin's lymphoma, second-line or salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation has been shown to improve progression-free and overall survival when compared to standard-dose chemotherapy alone.[1,2] Non-marrow ablative standard dose regimens are desirable in this setting to preserve stem cell number while debulking tumor mass. In this light, a regimen including gemcitabine, dexamethasone and cisplatin offers theoretic appeal. Each of these drugs singly or used in other combinations has been shown to have therapeutic benefit, and with only modest effect on marrow function.

Accordingly, Crump and colleagues from the National Cancer Institute of Canada performed a phase II trial in which 51 eligible patients with recurrent or refractory diffuse large B-cell lymphoma or variants (per REAL classification), measurable disease, and one previous chemotherapy regimen were enrolled. Treatment consisted of gemcitabine 1000 mg/m^2 intravenously (iv) on days 1 and 8, dexamethasone 40 mg orally on days 1-4, and cisplatin 75 mg/m^2 on day 1, every 21 days, as an out patient. The primary end point was a response after 2 cycles. At that point, responding patients either proceeded to stem cell transplantation (SCT) or continued on the GDP regimen for up to 6 treatment cycles.

The median age of patients enrolled was 57 years (range, 18-84) and most had diffuse large-cell lymphoma. After 2 cycles, there were 8 complete responses (CR, 16%) and 17 partial responses (PR, 33%), for an overall response rate of 49% (95% confidence interval [CI], 37-63%). The response rate after completion of all protocol chemotherapy (including those who received > 2 cycles of GDP) was 53% (11 CR, 16 PR).

Grade 3 and 4 neutropenia occurred in 33% and 39% of patients, respectively. Grade 3 and 4 thrombocytopenia occured in 24% and 4% of patients respectively. Seven patients (14%) experienced febrile neutropenia. Of the 35 patients younger than 66 years of age, 22 (63%) proceeded to SCT. Non-hematological toxicity included grade 2 or greater nausea and vomiting occurred in 14 (27%) and 11 (22%) respectively. Grade 1 or 2 ototoxicity occurred in 13 (25%), and was attributed to cisplatin. Thromboembolic events occurred in 7 (14%) patients, including a fatal pulmonary embolism in one. Of the 51 patients enrolled, 17 (33%) required hospital admission for either a complication of treatment (febrile neutropenia, dehydration) or disease. As planned a subset of these patients went on to receive autologous stem cell collection. Of 23 patients in which this approach was attempted, mobilization of sufficient stem cell number was successful in 22 (96%). Of the 22 in whom there were sufficient stem cells for transplant, one patient had progressive disease before transplant and the procedure was cancelled, and 21 received high-dose chemotherapy and autologous stem cell infusion. The median time to neurtophil recovery was: > 0.5×10^9/L was 10 days (range, 8-24 days) and the median time to platelet recovery > 20×10^9/L was 13 days (range, 8-28 days).

COMMENT BY WILLIAM B. ERSHLER, MD

The results of this multicenter Phase II trial demonstrate the use of the GDP regimen in patients with recurrent, aggressive NHL, particularly if autologous stem cell transplantation is under consideration. The regimen was moderately well tolerated and response rates are comparable to other regimens, including ifosfamide, carboplatin, and etoposide (ICE), and dexamethasone, high-dose cytosine arabosinide (ara-C), and

cisplatin (DHAP). The seeming advantage of GDP is the facility of administration (successfully administered as an outpatient in the great majority of patients in the current trial) and the relatively modest marrow toxicity, considering the aggressive disease being treated. The latter point is highlighted by the success at mobilizing stem cells in all but one of the patients for which this treatment was considered appropriate in this series.

The trial was small, and the results modest, yet the theoretical appeal of this combination and the relative ease of administration would seem to warrant a larger scale Phase III clinical trial, and it is encouraging to see that such a trial is currently underway (by the National Cancer Institute of Canada) comparing GDP and DHAP in this precise clinical setting (recurrent large cell lymphoma prior to stem cell transplant). In the meantime, practicing oncologists may feel familiar enough with the components of this regimen to use it under appropriate circumstances. ■

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Circulating Tumor Cells, Disease Progression, and Survival in Metastatic Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *The number of circulating tumor cells before treatment is an independent predictor of progression-free survival and overall survival in patients with metastatic breast cancer.*

Source: Cristofanilli M, et al. *N Engl J Med*. 2004;351:781-791.

In a prospective, multicenter study, Cristofanilli and colleagues tested 177 patients with clinically detectable metastatic breast cancer for levels of circulating tumor cells both before and after the initiation of various forms of therapy. The response to therapy was followed using standard clinical detection, but blood samples were also collected to determine the burden of tumor cells in the circulation. Cristofanilli et al found that the levels of circulating tumor cells at baseline, and at the first follow-up visit, were the most significant predictors of progression-free and overall survival. Cristofanilli et al note that this study was made possible by technological advances affording detection of circulating tumor cells. In this study, Cristofanilli et al utilized a newly developed approach called CellSearch System by Veridex. The system is based on enumeration of epithelial cells, which are separated from the blood by antibody-coated magnetic beads, and identified using fluorescent-labeled antibodies against cytokeratin.

All but 10 of the 177 patients had a minimal follow-up time of 38.7 weeks. Circulating epithelial cells were rare in healthy women and in patients with benign breast disease. The levels of circulating tumor cells at baseline, and at the first visit after the initiation of therapy, predicted outcome better than estrogen-receptor status, progesterone-receptor status, HER2/neu status, or type of therapy. Tumor burden at the first follow-up visit was somewhat more predictive of outcome than tumor burden before treatment. Indeed, for those receiving adjuvant hormonal intervention, circulating tumor cell count was only predictive for outcome after treatment and not before.

■ COMMENT BY SARAH L. BERGA, MD

The main hypothesis guiding this study is both simple in concept and exciting in potential. Cristofanilli et al asked whether the number of cancer cells detected in the blood before and after therapy correlated with tumor behavior and survival in patients with known metastatic breast cancer. A key barrier to testing this hypothesis was surmounted by the development of a robust technique to both identify and quantify tumor cells in the circulation. Since the study results rest so directly on technique, the study is in part a validation of this technique for detecting breast cancer cells in the circulation. Since there is no readily available gold standard for detecting breast cancer cells in the circulation, the manufacturers of the new approach had to depend in part on clinical outcomes for validation. Thus, Cristofanilli et al, out of necessity, had to simultaneously test both a biological hypothesis and a new technological development.

Assuming that Cristofanilli et al's study results are valid and replicable, where do the results made possible by this new technique put us? If the technique is highly sensitive and specific, then we potentially have a new method for refining the stage of the patient's breast cancer prior to initial therapy. Having this information might lead to important prognostic information. Such a technique might even allow us to predict tumor aggressiveness, or its return after an apparent remission. We also might be able to say with greater accuracy which patients do and do not need adjuvant therapy, what type of adju-

vant therapy would be best for a given breast cancer, or when to switch to another type of adjuvant therapy because the initial one chosen is not working. In short, this new technique might allow us to act on the notion that all breast cancers (and their hosts) are not the same. Given the many side effects of adjuvant therapy, having some way to individualize is truly exciting. The most far-reaching possibility, however, would be that such a technique could be used for advance detection of cancers, breast or otherwise, by a simple screening blood test. The widespread availability of a reliable and cost-effective screening technique would clearly be a welcome addition to our diagnostic armamentarium for those at high risk for breast or ovarian cancer, including those who carry BRCA1 and BRCA2 mutations. Realizing these clinical dreams hinges, in part, on whether tumor cells in the circulation adequately reflect the primary tumor across time and following intervention. Either way, though, this technique may help us to learn more about the multiple determinants of tumor behavior in vivo. ■

CME Questions

14. In the setting of recurrent, aggressive non-Hodgkin's lymphoma, treatment with the GDP regimen was shown to have an overall response rate of approximately:

a. 5%.
b. 25%.
c. 50%.
d. 75%.

15. With regard to breast density and subsequent breast cancer risk for women with DCIS who were treated with breast conserving surgery, an increase risk for subsequent ipsilateral breast cancer (either invasive or DCIS) was found for those:

a. with > 50% breast density by mammography.
b. with > 75% breast density by mammography.
c. with < 25% breast density by mammorgraphy.
d. None of the above

16. Which of the following factors is an independent predictor of adverse consequences following simultaneous (one-stage) resection of primary colorectal cancer and hepatic metastases?

a. Patient age of 66 years.
b. Histology revealing poorly differentiated adenocarcinoma.
c. Hepatic resection of 500 grams.
d. All of the above.

Answers: 14 (c); 15 (b); 16 (c)

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16. Publication of Statement of Ownership
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In Future Issues: More on More on Chemotherapy for Prostate Cancer

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, Travel Medicine Advisor.*

The FDA and Merck Fielding Concerns About Vioxx

Merck announced on September 30th that it is voluntarily withdrawing rofecoxib (Vioxx) from the worldwide market. The decision was based on data from the APPROVe (Addenomatous Polyp Prevention on Vioxx) trial, a company sponsored perspective randomized, placebo-controlled trial designed to assess whether the drug reduces the risk of colorectal polyps in patients with a history of colorectal adenomas. However, after 18 months of the study, patients on 25 mg of rofecoxib were noted to have an increased risk of cardiovascular events such as myocardial infarction and stroke, compared to those patients taking placebo. The FDA supported Merck's action and acknowledged that, while the risk to any individual on rofecoxib is small, the risk increases with continued use. The APPROVe trial showed that the risk of cardiovascular events with rofecoxib was twice that of placebo, according to information published on the FDA News website (fda.gov/bbs/topics/news/2004/NEW01122.html). Previous studies, including a recently reported Kaiser Permanente/FDA retrospective trial, showed the risk to be 3 times that of placebo. The FDA is investigating whether cardiovascular risk may be a class effect of COX-2 inhibitors (coxibs), and is reviewing data from similar trials with celecoxib (Celebrex) and valdecoxib (Bextra). Meanwhile, Merck is initiating a buy-back program for unused Vioxx prescriptions, reimbursing patients for their unused prescriptions. The withdrawal has enormous implications for the company and its shareholders, not only from the loss of nearly $2 billion in revenues from drug, but lost share value for the company stock and the risk of future legal action. It is estimated that 2 million patients in the United States were taking Vioxx at the time of the withdrawal, and over 84 million people worldwide have taken drug at some point since its approval in May 1999. The October issue of the *New England Journal of Medicine* has 2 scathing reviews of Merck and the FDA with regard to the approval and marketing of rofecoxib. Dr. Eric Topol of The Cleveland Clinic, who was one of the first to raise concerned about rofecoxib, calls for a full Congressional review of this case. The senior executives at Merck, and the leadership of the FDA, share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health (*N Engl J Med.* 2004;351:1707-1709). Dr. Garrett FitzGerald of the University of Pennsylvania suggests evidence has been there all along that coxibs, including celecoxib and valdecoxib, may promote cardiovascular disease by blocking prostaglandin I2, which inhibits platelet aggregation, promotes vasodilation, and prevents the proliferation of vascular smooth muscle cells in vitro. At the same time, coxibs have little effect on thromboxane A2, which is responsible for platelet aggregation.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com.

Traditional NSAIDs and aspirin block thromboxane production, accounting for their cardioprotective effects. Dr. FitzGerald states, "It is essential to determine whether cardiovascular risk is or is not a class effect." The burden of proof now rests with those who claim that this is a problem for rofecoxib alone, and does not extend to other coxibs." (*N Engl J Med*. 2004;351:1709-1711).

Erythromycin and the Risk of Sudden Death

Erythromycin may be associated with an increased risk of sudden death, according to new study in the *New England Journal of Medicine*. Oral erythromycin, which is extensively metabolized by cytochrome P-450 3A (CYP3A), prolongs cardiac repolarization, and has been associated with reports of torsades de pointes. Commonly used medications that inhibit CYP3A may increase plasma erythromycin levels, increasing the risk of ventricular arrhythmias and sudden death. Researchers from Vanderbilt reviewed data from a Tennessee Medicaid cohort that included more than 1.2 million person-years of follow-up and 1476 confirmed cases of sudden death from cardiac causes. The patients in the study were relatively young, with a mean age of 45. Seventy percent were female, and 58% were white. The multivariate adjusted rate of sudden death from cardiac causes among patients using erythromycin was twice as high as that among those who had not used any of the study antibiotic medications (incident-rate ratio 2.01; 95% CI, 1.08-3.75; $P = 0.03$). There was no increase in sudden death among patients using amoxicillin, or former users of erythromycin. For patients who were taking erythromycin with concurrent use of a CYP3A inhibitor (nitroimadazole antifungal agent, diltiazem, verapamil, or troleandomycin), the adjusted rate of sudden death was 5 times as high (incident rate ratio 5.35; 95% CI, 1.72-16.64; $P = 0.004$). The authors conclude that erythromycin should be avoided in patients who are taking CYP3A inhibitors (*N Engl J Med.* 2004;351:1089-1096).

Vaccine Shortage Putting Americans At Risk

Just as healthcare providers are about to start their annual flu vaccination program, British regulators have shut down Chiron Corporation's Liverpool flu vaccine manufacturing plant due to sterility problems. Chiron was expected to supply nearly 50 million doses of vaccine this year, half of the hundred million doses health officials expected to be administered to Americans this fall. Aventis, the other major supplier of vaccine, has told health officials that he could produce an additional million doses this year, but no more. Compounding the shortage, is the addition of 2 groups of patients recommended to receive the vaccine this year—children between the ages of 6 and 23 months (who require 2 doses 1 month apart) and pregnant women (or women who anticipate being pregnant during the flu season). Other high-risk patients include people over age 65, people in nursing homes, people with chronic illnesses, and those caring for people in these groups. Healthcare workers are also considered the highest priority for vaccination. The nasal flu vaccine, FluMist, does little to alleviate the shortage since it is only indicated for healthy children and adults between the ages of 5 and 49 years.

FDA Actions

The FDA will move ahead with warnings for many antidepressants stating that the drugs sometimes raise the risk of suicidal behavior in youth. The recommendation comes after an agency advisory panel, on a split vote, recommended a Black box warning. The agency may not go that far, however, since some advisors were concerned that warnings may discourage treatment of depressed children and teens who can benefit from antidepressants medications. The drugs subject to the warning are those with the brand names Prozac, Paxil, Wellbutrin, Zoloft, Celexa, Effexor, Luvox, and Remeron.

The recently approved antidepressant duloxetine (Cymbalta) has received FDA approval for treatment of pain associated with diabetic neuropathy. This is the first drug approved for this indication in this country. In 2 studies submitted to the FDA, the drug reduced 24-hour average pain levels, compared with placebo, in patients who had diabetes for an average of 11 years, and had neuropathic pain for average of 4 years.

The FDA has approved a new extended release formulation of hydromorphone for the management of persistent moderate-to-severe pain in patients requiring continuous, round-the-clock opioid pain relief for extended periods of time. The product is an extended release formulation that can be dosed once a day, and will be available in 12, 16, 24, and 32 mg capsules. The drug is only recommended for patients already receiving opioid therapy who have demonstrated opioid tolerance, and who require a minimum total daily opioid dose equivalent to 12 mg of oral hydromorphone. It will be marketed by Purdue pharmaceuticals with the trade name Palladone.