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

ABSTRACT & COMMENTARY

Improving Survival Rates by Surgical Resection of Colorectal Liver Metastases

By William B. Ershler, MD

SYNOPSIS: In a retrospective analysis of aggressive two-stage hepatic resection of colorectal metastases, survival was 51% at 5 years compared to only 15% for comparable patients treated with chemotherapy alone. The complexity of the surgical approach and the advent of potentially more effective systemic therapies highlight the need for a definitive randomized trial before such an approach is assimilated into community practice.

SOURCE: Brouquet A, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: Response-based selection and complete resection outcome. *J Clin Oncol* 2011;29:1083-1090.

Advances in surgical oncology have resulted in new and more aggressive approaches to metastatic disease in certain clinical settings, such as for patients with colorectal cancer metastatic to the liver.[1] One such advance is the two-stage resection (TSR),[2] which has been shown in selected series to produce impressive survival rates.[2-4] However, the generalizability of such an approach is under question because of concerns that the dramatically improved survival rates in operated patients compared to those treated with chemotherapy alone reflected a selection bias. That is, were patients selected for surgery those with more favorable prognostic features? Optimally, this would be addressed in a randomized clinical trial. However, short of that, the current report describes outcomes for well-matched patients treated at a single institution either with aggressive surgical resection of colorectal liver metastases (CLM) by the two-stage procedure or chemotherapy alone.

For this, data on patients undergoing resection were compared to matched patients receiving chemotherapy alone. Thus, the non-surgical patients had colorectal metastases with liver-only disease, a prior objective response to chemotherapy, and were alive 1 year after chemotherapy initiation. The investigators used intent-to-treat analysis. In the majority of patients who were candidates for and opted for TSR, the program included limited resection of CLM located in the left liver followed by right portal vein embolization 1 to 2 weeks later and then an extended right hepatectomy.

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Clinical Oncology [ALERT]

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Sixty-five patients underwent the first stage of TSR; 62 patients fulfilled the inclusion criteria for the medical group. TSR patients had a mean of 6.7 ± 3.4 CLM with mean size of 4.5 ± 3.1 cm. Nonsurgical patients had a mean of 5.9 ± 2.9 CLM with mean size of 5.4 ± 3.4 cm (not significant). Forty-seven TSR patients (72%) completed the second stage of the procedure. Progression between stages was the main cause of non-completion of the second stage (61%). After 50 months median follow-up, the 5-year survival rate was 51% in the TSR group and 15% in the medical group (P = 0.005). In patients who underwent TSR, non-completion of TSR and major postoperative complications were independently associated with worse survival.

COMMENTARY

It is clear from the data presented that TSR is associated with excellent outcome in patients with advanced CLM. Certainly, this is the result both of surgical resection and optimal patient selection. Those taken to surgery have demonstrable chemotherapy-induced tumor shrinkage, perhaps reflecting a "responsive" population. The authors are credited for making efforts to identify suitable controls with many of the same prognostic factors. However, the fact remains that for one reason or another these patients were treated differently, and it is not clear what factors led to the decision to operate on some and not on others. Could it be that those treated medically had more comorbidity or some other factor that would negatively influence prognosis?

Defining the role of surgical resection for CLM remains to be fully established, and of course this would best be accomplished by an appropriately randomized clinical trial. The data presented are provocative and provide substantial rationale for such a trial. This would be particularly important in light of the advances in systemic management of metastatic colorectal cancer with more effective chemotherapy (oxaliplatin and irinotecan) as well as monoclonal antibodies targeting vascular endothelial growth factor (bevacizumab) and epidermal growth factor receptor (cetuximab and panitumumab). Another variable worthy of consideration is the overall complexity of the two-step surgical procedure involving operating twice on an already diseased liver. Although the authors report a 6% 90-day mortality rate and a 50% morbidity rate after the second stage of the procedure, these figures are likely to be less optimal in the hands of less experienced surgeons.

Thus, the M.D. Anderson experience with two-stage resection of CLM is quite favorable but further study is warranted before such an approach is routinely undertaken in the community. ■

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ABSTRACT & COMMENTARY

Colorectal Adjuvant Chemotherapy: Timing Is Something

By William B. Ershler, MD

SYNOPSIS: In a retrospective review, delay beyond 60 days in initiating adjuvant chemotherapy after surgery for colorectal cancer was associated with poorer overall survival. Although factors such as surgical complications or the existence of comorbidities may explain the delays for

some of the cases, other "administrative" factors, such as delays resulting from insurance authorizations or referral setbacks, are to be avoided, if at all possible.

SOURCE: Bayraktar UD, et al. Does delay of adjuvant chemotherapy impact survival in patients with resected stage II and III colon adenocarcinoma. *Cancer* 2011;117:2364-2370.

It's a commonly held notion that prompt institution of adjuvant chemotherapy for patients with newly diagnosed colon cancer after surgical resection is optimal, although this primarily is based on hypothetical reasoning, perhaps accumulated experience but not on well-controlled clinical investigation. It has been held that during recovery from surgery there is enhanced angiogenesis and transient depression of immune function resulting in both a period of enhanced growth of microscopic residual disease and a window of opportunity to eradicate proliferating cells with effective cytotoxic chemotherapy.[1-3] Accordingly, most clinical trials of adjuvant chemotherapy call for a minimal delay after surgery before the initiation of treatment and exclude enrollment if there has been a delay of 8 weeks or more. Yet, it remains unclear from the published literature to what extent the time to initiating chemotherapy influences the overall benefit.

Capitalizing on a rich database from Jackson Memorial Hospital and the Sylvester Comprehensive Cancer Center in Miami, Bayraktar and colleagues performed a retrospective analysis to address this question. Patients with stage II-III colon adenocarcinoma who received adjuvant chemotherapy at either of these two centers were identified through the institutional tumor registry. Time to adjuvant chemotherapy, overall survival (OS), and relapse-free survival (RFS) were calculated from the day of surgery. Patients with rectal cancer were not included, nor were patients who had adjuvant chemotherapy started beyond 120 days or patients who had less than 3 months of follow-up. Patients were dichotomized into early (time to adjuvant chemotherapy ≤ 60 days) and late (time to adjuvant chemotherapy > 60 days) treatment groups. OS and RFS were compared using log-rank test and multivariate analysis by the Cox proportional hazards model.

Of 186 patients included in the study, 49 (26%) had received adjuvant chemotherapy > 60 days after surgical resection. Thirty percent of the delays were system-related (e.g., late referrals, insurance authorizations). Time to adjuvant chemotherapy > 60 days was associated with significantly worse OS by both univariate analysis and a Cox proportional hazards model (hazard ratio, 2.17; 95% confidence interval, 1.08-4.36). Although difference in RFS between the two groups favored time to adjuvant chemotherapy < 60 days, this did not reach statistical significance.

COMMENTARY

There are several reasons adjuvant chemotherapy might be delayed. Some are administrative, such as insurance authorization or delayed clinic appointments. However, others, such as delays that result from postoperative complications or the need to attend to comorbidities prior to the induction of chemotherapy, might, in themselves, predict a less favorable outcome based either upon the higher likelihood of greater residual microscopic disease (such as might be expected after surgery associated with perforation) or dose reductions/schedule delays that are more likely to exist among those with significant comorbidities. In the current report, there was a trend (although not statistically significant) that patients who were married were more likely to start adjuvant chemotherapy within 60 days, a finding consistent with other reports.[4] However, there was no association between adjuvant chemotherapy delay and race/ethnicity or among those who had delays from diagnosis to surgery.

The current report provides an inkling that time itself is a relevant factor inasmuch as by multivariate analysis delays that resulted from surgical complications or administrative factors that were controlled (covariates in the multivariate analysis). It was apparent that overall survival was better for most subgroups, although with the relatively small sample size, statistical significance was reached for only a few. Unfortunately, the important issue of comorbidities could not be addressed adequately because of the small numbers and incomplete data, so it remains unclear to what extent delays in the initiation of adjuvant chemotherapy can explain decrements in survival for those with additional medical problems. But for the group as a whole, the analysis indicates that delays in starting adjuvant chemotherapy beyond 60 days is associated with less optimal overall survival.

The true impact of delayed adjuvant therapy only would be addressed adequately by a prospective, controlled clinical trial, and such is not likely to be undertaken for ethical reasons. Nonetheless, retrospective analyses such as this are useful in identifying factors that might be associated with delays, some of which may be correctable.

Although supporting evidence is incomplete, it remains prudent to initiate adjuvant therapy within 2 months after surgery. ■

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ABSTRACT & COMMENTARY

CML Treatment in the Elderly: Imatinib Levels the Playing Field

By Andrew S. Artz, MD, MS

Division of Hematology/Oncology, University of Chicago

Dr. Artz reports no relationships to this field of study.

SYNOPSIS: Older age is an adverse prognostic factor for chronic myeloid leukemia (CML) in the pre-tyrosine kinase era. The authors evaluated the influence of age on outcomes among 559 chronic-phase CML patients treated with imatinib. Of the 115 patients 65 years and older (21%), complete cytogenetic and molecular response rates did not differ. However, progression-free survival (62% vs 78%) and overall survival were worse (75% vs 89%) for older adults because of a significant increase in deaths while in hematologic remission. Imatinib overcomes the negative prognostic impact of age on disease response for CML chronic phase.

SOURCE: Gugliotta G, et al, on behalf of the Gruppo Italiano Mallattie Ematologiche del l'Adulto CML Working party. Frontline imatinib treatment of chronic myeloid leukemia: No impact of age on outcome, a survey by the GIMEMA CML Working Party. *Blood* 2011;117: 5591-5599.

Chronic myeloid leukemia (CML) is characterized by the 9;22 translocation, creating a constitutively activated BCR/ABL tyrosine kinase. BCR/ABL inhibition by imatinib mesylate (Gleevec) and other tyrosine kinases have revolutionized CML.[1] Prognostic models developed prior to imatinib demonstrate older age adversely affects response rates and survival.[2,3] The precise reasons for inferior survival and worse response may be multifactorial including worse tolerance to therapy, delayed medical care, non-hematologic comorbid conditions, and/or biologic differences in disease. The recent series reviewing the interaction between imatinib and age reported mixed results. Rosti reported lower response rates to imatinib for patients 65 years and older but no difference in survival.[4] M.D. Anderson assessed 747 patients at different CML stages and found no difference in response or survival after imatinib therapy for adults 60 years and older, although follow-up was short.[5]

In this report, the authors analyzed the impact of older age on outcome among 559 patients with early chronic phase CML after initial therapy with imatinib. Results were collated from three front-line clinical trials dosing imatinib at 400 mg to 800 mg daily. The median age was 52 years (range 18–84 years) with 115 (21%) 65 years of age or older. Fewer older adults were assigned to low Sokal Risk score as expected, as the Sokal score models older age as an adverse prognostic factor. Complete hematologic response at 3 months was 97% for older adults and 96% for younger adults. Complete cytogenetic remission (CcyR) did not differ at 6, 12, or 18 months by age. Specifically, CCyR at 12 months was 78% for older adults and 77% in younger adults and major molecular response at 12 months was 58% and 59% for older and younger adults, respectively. Loss of CCyR occurred in 14% of older adults and 8% of younger patients (P = 0.084).

However, 6-year event-free survival was inferior for older adults at 55% compared to 67% in younger adults (P = 0.006). Similarly, older age suffered worse failure-free survival, progression-free survival, and overall survival (P < 0.0001 for OS). Imatinib failure rates related to primary or secondary resistance did not differ by age. However, older patients died more often while in complete hematologic response at 15% vs 3% in younger patients (P < 0.0001). Deaths from disease progression occurred in 5% of older patients and 3% of younger patients. The causes for deaths in older patients varied.

COMMENTARY

Historically, older age conferred a worse prognosis for CML in terms of inferior response and survival. In the prior era of more toxic treatments such as inteferon-alpha, worse tolerance and adverse disease biology were implicated. Tyrosine kinase

inhibitors, such as imatinib, now represent the mainstay of treatment for CML resulting in high response rates and low rates of serious toxicities.

This report derived from three consecutive upfront trials of imatinib at 400 mg to 800 mg for chronic-phase CML provide compelling evidence that older age alone does not impair response rates in imatinib-treated patients. Specifically, rates of complete hematologic response, complete cytogenetic response, major molecular response, and loss of response did not differ for those 65 years and older relative to their younger counterparts. Overcoming the negative age-related response to prior CML therapies could be from better tolerance. Alternatively, imatinib may diminish negative biologic features as has been demonstrated for imatinib neutralizing the poor prognosis of derivative chromosome 9.[6]

The negative impact of older age on survival persisted because of a greater number of deaths in disease control (i.e., complete hematologic remission). The authors reasonably surmise this represents a greater burden of concomitant illnesses in older adults. They astutely observe that imatinib therapy also could result in serious adverse events that might be more likely to occur in older adults, although no clear pattern existed among causes of death. Cardiac causes were uncommon. The authors should be credited not only with a comprehensive comparison in a homogenous cohort of early chronic phase CML but also for meticulously tabulating the causes of failure. Other series evaluating older age and outcomes for CML after imatinib therapy evaluated more heterogeneous populations. The largest series from M.D. Anderson Cancer Center reported complete cytogenetic remission in 87% of patients 60 years and older compared to 79% in younger adults but also inferior survival.[6]

A practical implication is that imatinib may be underused in older CML patients. Epidemiologic series show that imatinib use dramatically declines with older age, suggesting some older adults are not offered treatment because of concerns about toxicity or low response rates.[7] These data offer reassurance that imatinib maintains efficacy in older adults. An obvious caveat is that the "oldest" old (i.e., older than 80 years) and less fit elderly adults typically are not enrolled in clinical trials. Thus, one cannot necessarily infer to this population.

In summary, imatinib therapy achieves similar high rates of disease control in younger and older adults for early chronic phase CML. Long-term survival is worse and attributable to a greater number of deaths as expected in older adults while in disease control. Older age should not be a barrier to offering imatinib therapy for chronic phase CML. ■

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ABSTRACT & COMMENTARY

Population Screening for the Early ID of Prostate Cancer

By Jerome W. Yates, MD

Hematology/Immunology Unit, National Institute on Aging, NIH

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

SYNOPSIS: To assess whether screening for prostate cancer reduces prostate-specific mortality, a population-based, randomized, controlled trial for a random sample of men between the ages of 50 to 69 in a single city were screened every third year from 1987 to 1996. There was no significant difference in the rate of death from prostate cancer for the screened group compared to the control group after 20 years of follow-up.

SOURCE: Sandblom G, et al. Randomised prostate cancer screening trial: 20 year follow-up. *BMJ* 2011;342:1539-1545.

The use of prostate specific antigen (PSA) as a screening tool to identify men with cancer of the prostate gained momentum rapidly in the late 1980s. Its enthusiastic acceptance as a suitable test for identifying early prostate cancer rapidly gained acceptance among members of the urological community because elevations (> 4 ug/L) led to prostate biopsies that often found localized prostate cancer. The benefit of a prostate cancer screening program has yet to be demonstrated in a randomized clinical trial in which fewer prostate cancer deaths are observed among those screened.[1]

Examining the relative success of screening, diagnostic, and treatment programs for prostate cancer is complicated. Problems with "minimal risk disease" characterized by low-volume tumors with low Gleason scores and little chance of causing death provides a major challenge.[2] Based on an autopsy series of men, subclinical or latent prostate cancer appears as early as the second decade of life and increases linearly thereafter.[3] A 70-year-old man undergoing prostate biopsy has nearly a 70% chance of yielding cancer. There also is a linear increase in mean tumor volume and an increasing Gleason score (measure of malignant potential) with age.[3]

[Examining the relative success of screening, diagnostic, and treatment programs for prostate cancer is complicated.]

In the current report, Sandblom and colleagues address the prostate cancer specific survival in both screened and not screened cohorts. They report that the risk ratio for death from prostate cancer in the screened group was 1.16 with the 95% confidence intervals extending from 0.78 to 1.73, clearly not statistically significant. Furthermore, there was no increase in prostate cancer survival for men for whom cancer was detected by screening.

COMMENTARY

This is an important piece of work. Treatment with curative intent of minimal risk disease carries the same risk for complications as it does for those with more advanced disease. These complications include urinary incontinence, proctitis, and sexual impotence, any or all of which affect quality of life in a negative way. Unnecessary overtreatment is a serious problem that can result from population-based screening for prostate cancer.[4]

Because this article reflects the rigor of a population-based, randomized clinical trial with an impressive population sample, excellent compliance, a uniform intervention, and outstanding follow-up information providing outcome data, the conclusions are appropriate. The screened population had a slightly increased incidence of prostate cancer probably reflecting the detection of a larger number of indolent or minimal risk cancers. All men were managed in the same urological unit following their diagnosis for prostate cancer, minimizing the potential for treatment bias leading to a prostate cancer death differential between the screened and the control group.

Screening enthusiasts have done a great disservice to the medical community by using surrogate endpoints such as "down-staging" and increased survival (potentially the result of length bias — picking up slowly progressing disease and lead time bias, picking up disease earlier in its course without changing the overall course of the disease, or picking up indolent disease that will not progress). Physicians are stimulated by disease discovery, but it is clear that not all with elevated PSA or even histological changes consistent with a diagnosis of cancer will progress to clinically important disease. It is hoped that new molecular techniques will provide more precision in identifying truly "malignant" from indolent prostate cancer. Until then, PSA should not be recommended for population screening for prostate cancer.

Willet Whitmore, a urological surgeon, addressed the heart of the problem: "The quandary in prostate cancer: Is cure necessary in those for whom it is possible and is cure possible in those for whom it is necessary?"[5] Some overtreatment may be necessary, but data from a variety of studies indicate population screening using PSA is not appropriate. ■

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RAPID REVIEW

Extranodal Marginal Zone Lymphoma

By William B. Ershler, MD

The term marginal-zone lymphoma (MZL) refers to three distinct but closely related lymphoprolferative disorders: mucosa-associated lymphoid tissue (MALT) lymphoma (extranodal MZL), splenic MZL, and nodal MZL. Although all three are derived from a common cell of origin (marginal zone B cell), they are likely to display different clinical manifestations. The common cell of origin is derived from the periphery of the lymphoid B-follicle. A feature of this micro-anatomic location is the exposure to an influx of antigens (e.g., in the gastric mucosa, spleen, or lymph nodes) and there has been an increased understanding of the role of inflammation and infection in the pathogenesis of these disorders, most notably for gastric MALT, for which the association with *Helicobacter pylori* is now irrefutable.[1-3]

In fact, *H. pylori* eradication therapy leads to complete lymphoma regression in about 80% of cases with early-stage disease.[4] However, the link between infection and MZL is less clear for non-gastric variants. Nonetheless, when extranodal MZL occurs at other sites (e.g., skin, lacrimal gland, ocular adnexa, small intestine) consideration of other chronic infections, such as *Borrelia burgdorferi* (skin),[5] *Chlamydophila psittaci* (ocular),[6] or *Campylobacter jejuni* (small intestine),[7] should be pursued. There is also an association between MALT lymphoma and certain autoimmune disorders such as Sjogren syndrome and systemic lupus erythematosus.[8] The strength of these associations is variable. Nonetheless, a common thread in the pathogenesis of extranodal MZL is chronic antigenic stimulation and inflammation. Laboratory investigations have revealed a central role for aberrant NFkB activation in the pathogenesis of MALT lymphoma in certain cases.[9]

Cytogenetic Features

Although a number of chromosomal abnormalities have been associated with MALT lymphoma, the most common is t(11;18)(q21;q21),[10] which occurs in up to 50% of patients with gastric MALT lymphoma, less frequently in pulmonary MALT lymphoma, but only rarely in other extranodal MZL.[11] Among those with gastric MALT lymphoma, the presence or absence of t(11;18)(q21;q21) does not relate to morphology or immunophenotype. However, there has been some suggestion that those who are t(11;18)(q21;q21)+ are more resistant to complete regression after *H. pylori* eradication.[12]

Additional cytogenetic changes have been described for extranodal, splenic, and nodal MZL, and these include trisomies 3 and 18, occurring in anywhere from 15% to 60% of cases. Other cytogenetic findings have been quite heterogeneous and there are no unique abnormalities currently documented.

Treatment Considerations

Patients with gastric MALT lymphoma most commonly present with non-specific gastrointestinal complaints, and upper endoscopy often reveals gastritis or ulcer or less commonly a gastric mass. The diagnosis hinges on gastric biopsy and the demonstration by histochemistry of *H. pylori*. The fluorescence in situ hybridization demonstration of t(11;18)(q21;q21) may be useful for identifying those who might not respond to antibiotic therapy alone. For most patients, *H. pylori* eradication results in complete regression of the MALT lymphoma and most of these regressions are durable. Standard anti-helicobacter treatment, including proton pump inhibitor plus antibiotics (e.g., clarithromycin plus amoxicillin or tetracycline, metrinidizole with bismuth subcitrate) is sufficient. However, close follow-up is recommended with repeat endoscopy and biopsies at 2 or 3 months. For some with minimal residual disease (if *H. pylori* is confirmed to be eradicated), observation alone is reasonable as long as patients can be followed closely. The long-term risk for transformation to more malignant lymphoma is less common for gastric MALT lymphoma than for other indolent histologies.[13]

For patients with persistent disease after *H. pylori* treatment, excellent disease control (for those with Stage I or II disease) has been achieved by radiation therapy, particularly with modern treatment plans that include three-dimensional conformal and intensity-modulated radiotherapy. For those with systemic disease, immunotherapy with rituximab with or without chemotherapy has been effective. For patients with non-gastric MZL, particularly for those in whom chronic infection is not defined, treatment recommendations follow those established for indolent B-cell lymphoma. Radiation therapy is recommended for those with localized

disease. However, systemic therapy with rituximab with or without chemotherapy should be considered for those with more widespread involvement. Clinical trials have demonstrated that response rates as high as 70% can be achieved with rituximab alone.[14] ■

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CME Questions

1. Two-stage resection of colorectal iver metastases was found by M.D. Anderson investigators to result in a 5-year survival rate of:

a. 5%.
b. 23%.
c. 51%.
d. 75%.

2. How do patients 65 years and older fare on imatinib therapy for chronic phase CML compared to younger adults?

a. Inferior rates of complete cytogenetic remission at 12 months
b. Greater likelihood of drug discontinuation due to non-adherence
c. Worse long-term overall survival
d. No difference in 6-year event-free survival

3. After 20 years of follow-up, men who were screened annually by PSA determination compared to those who were not screened were found to have:

a. statistically significant more diagnoses of aggressive prostate cancer.
b. statistically significant higher relative risk of death from prostate cancer.
c. None of the above.

CME Objectives

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

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
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Managing Glioblastoma in Elderly Patients

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The essential monthly primary care update

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COPD in Never Smokers

Source: Lamprecht B, et al. *Chest* 2011; 139:752-763.

Unless there is another overt cause, such as occupational exposure to toxic inhalants, we generally expect chronic obstructive pulmonary disease (COPD) to be secondary to cigarette smoking. The pulmonology literature consistently suggests that a substantial minority — at least 20% — is NOT related to cigarette smoking. This multinational survey by Lamprecht et al provides a fresh appraisal of the burden of COPD unrelated to smoking.

The Global Initiative for Obstructive Lung Disease (GOLD) guidelines were used to define COPD through spirometry. Primary cigarette smoking, exposure to secondary smoke, occupational exposure, and biomass exposure (for instance, cooking or home heating using wood, coal, dung, or crop residue) were all queried among 10,000 subjects from 14 countries.

Of the 4291 never smokers, 12.2% fulfilled GOLD criteria for COPD. Of all persons ultimately defined as meeting COPD criteria, just over one-fourth were never smokers. Women were disproportionately represented in the group of persons with moderate-severe COPD. It has been suggested that women may have greater susceptibility both to tobacco smoke as well as other potentially toxic inhalants.

COPD is now the third most common cause of death in America. Pulmonologists have suggested that COPD remains underdiagnosed. Based on these results, the authors suggest that symptomatic persons, even if never smokers, should be screened for COPD. ■

Early Prostate Cancer: Prostatectomy vs Watchful Waiting

Source: Bill-Axelson A, et al. *N Engl J Med* 2011;364:1708-1717.

The management of early prostate cancer (PCA) remains controversial. Although surgical and radiation interventions offer the opportunity for cure, many more men with early PCA die with the disease than from it. Were definitive interventions without risk, there likely would be little discussion about whether to intervene; however, because the potential consequences of intervention are significant (e.g., incontinence, erectile dysfunction), clarification of the risk:benefit ratio is critical.

A randomized multinational study of subjects from Sweden, Finland, and Iceland (n = 695) randomized men < 75 years of age with localized, moderately well to well-differentiated prostate cancer to either radical prostatectomy or watchful waiting. Men were followed for 12.8 years.

At 12.8 years, all-cause mortality was statistically significantly less in the surgery group (166/347) than the watchful waiting group (201/348). Similarly, PCA-related death was superior in the surgically treated group (14.6% vs 20.7%). Benefits were clear from men < 65 years of age, but only a trend toward benefit (results not statistically significant) could be determined from the data in older men, possibly because of the smaller number of men in this age group.

Adverse effects of surgery were substantial. For instance, at 1 year, 32% of men had incontinence and 58% had impotence. Younger men with early PCA appear to enjoy mortality benefit from surgical intervention, though at a substantial adverse event cost. Competing causes of death in older men diminish the relative benefits of surgery. ■

Dietary Vitamin D and Incident Diabetes

Source: Gagnon C, et al. *Diabetes Care* 2011;34:1133-1138.

The beta cells of the pancreas possess a vitamin D receptor, so perhaps we should not be surprised that vitamin D might be associated with diabetes (DM). Preliminary evidence has suggested that dietary vitamin D (VTD) might be associated with risk for DM, but prior to this report, no large population study has provided sufficient information to be definitive.

Gagnon et al researched subjects involved in the AusDiab studies, which included 11,247 noninstitutionalized adults free of DM at baseline who underwent a 75 g oral glucose tolerance test (GTT) at baseline. Five years later about half (6537) of these had a repeat GTT, of which 80% were still not diabetic.

The investigators found a linear relationship between reported dietary VTD and incident DM over a 5-year interval: for every 25 nmol/L increase in VTD, there was a 24% reduced risk of DM. Also studied in this same data set was calcium intake, which did not correlate with incident DM. Subjects in the top quartile of VTD intake enjoyed a 44% risk reduction for incident DM.

Because these are observational data, causation cannot be established. Prospective, randomized, placebo-controlled trials of VTD supplementation will be necessary to confirm the preventive capacity of VTD. ■

Functional Cobalamin Deficiency in Diabetes

Source: Solomon LR. *Diabetes Care* 2011;34:1077-1080.

It has been suggested that as many as 30% of senior citizens have so-called functional cobalamin deficiency (FCD), defined as the presence of elevated metabolites such as methylmalonic acid in the face of ostensibly normal cobalamin levels. Since methylmalonic acid should accumulate primarily in the circumstance of vitamin B12 insufficiency, there appears to be some functional deficiency in cobalamin, manifested as increased levels of methylmalonic acid.

The intersection of diabetes with FCD occurs because previous trials have noted that diabetics comprise up to one-third of subjects experiencing improvements in neuropathic signs with vitamin B12 supplementation, and the vast majority of these subjects (88%) did not have decreased vitamin B12 levels.

To better define the epidemiologic profile of FCD, a retrospective review of patients evaluated for cobalamin deficiency from 1993-2005 characterized levels of cobalamin in relation to methylmalonic acid. Because renal insufficiency is associated with increases in methylmalonic acid, creatinine > 1.4 mg/dL was an exclusion criterion.

Among nondiabetics there was an inverse relationship between methylmalonic acid and cobalamin. Among diabetics, however, increasing cobalamin levels were not associated with decreasing methylmalonic acid, suggesting that there was a relative cobalamin resistance.

Equally noteworthy, neuropathy was much more frequent in persons with elevated methylmalonic acid than without (62% vs 18%) and more than 85% of persons treated with pharmacologic doses of cobalamin experienced improvement in neuropathy.

There is substantial controversy over the existence of functional cobalamin deficiency. Considering that cobalamin supplementation has no known important toxicity, clinicians may wish to re-examine the issue of cobalamin treatment for diabetic subjects with elevated levels of methylmalonic acid, even in the face of normal cobalamin levels. ■

Should Leukotriene Antagonists Have Higher Priority for Asthma Control?

Source: Price D, et al. *N Eng J Med* 2011;364:1695-1707.

Current asthma guidelines suggest that once an asthma patient has progressed to the stage of persistent asthma (even mild-persistent asthma), inhaled corticosteroids (ICS) should be the preferred initial "controller" (maintenance) medication. Nonetheless, comparator trials of leukotriene inhibitors (LKT) with ICS have produced inconsistent findings, sometimes indicating superiority of ICS, but other times suggesting equal efficacy of the two classes. Because concerns about adverse effects of ICS in obstructive airways diseases have persisted for several decades, the absence of similar concerns with LKT agents promotes consideration of how to maximize their positive potential.

Two trials comprise the data reported in this publication. In the first, persons initiating controller therapy for persistent asthma (n = 306) were randomized to either ICS or LKT. In the second trial, asthma subjects who had already received ICS for controller medication but who required advancement of pharmacotherapy (n = 352) were randomized to either LKT or long-acting beta agonist (LABA). The primary outcome was the score on the Mini Asthma Quality of Life Questionnaire at 2 months. Secondary outcomes included the same questionnaire results at 2 years and frequency of asthma exacerbations.

At 2 months, the LKT proved equivalent to ICS as initial therapy, and equivalent to LABA as add-on treatment. At 2 years, although not able to achieve the statistical threshold defining equivalence, the outcomes were very similar. There was no difference in the frequency of exacerbations between LKT and ICS or between LKT and LABA when added to ICS. There was no placebo control in this trial, and the trial was open label. Nevertheless, these data suggest that in a "real world" setting, the efficacy of LKT in asthma may have been underestimated. ■

Selenium Impacts Orbitopathy in Graves Disease

Source: Krassas GE, et al. *N Eng J Med* 2011;364:1920-1931.

Ocular abnormalities associated with Graves disease are sometimes called Graves' orbitopathy (GORB) and occur in as many as half of Graves' disease cases. Treatments for GORB include glucocorticoids and irradiation, but are generally reserved for moderately severe disease. Mild GORB has been shown to spontaneously regress (20%), remain stable/unchanging (65%), or advance (15%). Hence, a safe intervention to prevent advancement of GORB would be desirable. The antioxidant effects of selenium led to consideration of its potential favorable impact upon GORB.

This controlled trial randomized patients (n = 107) to selenium sulfide 100 mcg twice daily or placebo for 6 months. GORB evaluation was done at baseline, 3, 6, and 12 months. The primary outcome was the percentage of patients improving from baseline. The study hypothesis was that active treatment would improve the number of persons with GORB regression by 25%: from 20% (as seen in naturalistic follow-up of untreated GORB) to 45%.

By 6 months, there was a statistically significant improved quality of life and regression of GORB, which was reconfirmed at 12 months. There were no serious adverse effects seen with selenium.

Although it would have been nice to have seen selenium levels before and after treatment, and hopefully a correlation between selenium repletion and outcomes, these preliminary data are still quite supportive of a

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PHARMACOLOGY WATCH

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Two New Drugs Approved for Treatment of Hepatitis C

In this issue: Two new drugs for treatment of hepatitis C; NSAIDs and myocardial infarction risk; AIM-HIGH clinical trial stopped; and FDA actions.

Two new drugs for hepatitis C

The FDA has approved two new drugs for the treatment of hepatitis C — the first new drugs to be approved in years. The approvals came within days of each other, pitting the two drugs (and their companies' marketing departments) against each other in this multibillion dollar market. Both drugs are protease inhibitors and both have similar indications. First to be approved was Merck's boceprevir (Victrelis), which is indicated for adults with hepatitis C who still have some liver function and who either have not been treated previously with drug therapy or who have failed drug therapy. Boceprevir is approved for use in combination with peginterferon alpha and ribavirin. The approval was based on two phase 3 clinical trials of 1500 adults in which two-thirds of patients in the boceprevir, interferon, and ribavirin treatment group experienced a significantly increased sustained virologic response at 24 weeks compared to 38% with interferon and ribavirin alone. Boceprevir is taken orally three times a day with food. The second drug approved was Vertex Pharmaceutical's telaprevir (Incivek), which also was approved for patients with hepatitis C who either have not received interferon-based drug therapy or who have not responded adequately to prior therapies. Telaprevir is also approved for use with peginterferon alpha and ribavirin. Approval was based on three phase 3 clinical trials of over 2000 adults. In previously untreated patients, 79% of patients in the telaprevir group experienced a sustained viral response compared to 46% for standard treatment. Most patients experienced virologic response at 24 weeks suggesting that treatment times may be reduced from 48 weeks to 24 weeks. Telaprevir is also taken orally three times a day with food. Both drugs are approved to treat genotype-1, the most common form of hepatitis C and the most difficult to treat. The drugs have similar side effects, which include anemia and serious rashes. Several other drug manufacturers have similar drugs in the pipeline with approval expected within the next year or two. It is estimated that about 170 million people worldwide and 3.2 million Americans are infected with chronic hepatitis C, which is the most common cause of progressive liver disease leading to liver transplant. Telaprevir is expected to cost nearly $50,000 per treatment course, while bocepavir is expected to cost between $26,000 to $48,000 per treatment course depending on the duration. ■

NSAID use in patients with prior MI

A new study points out the risk of nonsteroidal anti-inflammatory drug (NSAID) use in patients who have had a myocardial infarction (MI) — suggesting that even brief use increases the risk for death and recurrent MI. Researchers from Denmark reviewed the records of nearly 84,000 patients who were admitted with first time MI and their subsequent NSAID use. The risk of death and recurrent MI was correlated to the duration of NSAID treatment. From 1997-2006, 42.3% of patients received NSAIDs. There

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were more than 35,000 deaths or recurrent MIs in the cohort of whom 43% had filled a prescription for an NSAID. Use of an NSAID was significantly associated with an increased risk of death or recurrent MI at the beginning of treatment (hazard ratio [HR] 1.45; 95% confidence interval [CI], 1.29 to 1.62) and persisted throughout the NSAID treatment course (HR 1.55; 95% CI, 1.46 to 1.64 after 90 days), returning to baseline soon after stopping the drug. The risk of death or recurrent MI varied with different drugs and was somewhat higher with increased COX-2 selectivity. Diclofenac was associated with the highest risk (HR 3.26; 95% CI, 2.57 to 3.86). Duration of therapy was also reviewed with diclofenac causing an increased risk from the beginning of treatment and persisting throughout the treatment course. Ibuprofen showed an increased risk when used for more than one week, whereas celecoxib showed an increased risk after 14-30 days of treatment. Naproxen was not associated with a statistically significant increased risk of death or MI for the entire treatment duration. The authors conclude that short-term treatment with most NSAIDs is associated with increased cardiovascular risk. This suggests that there is no apparent safe therapeutic window for NSAIDs in patients with prior MI and "challenge the current recommendations of low-dose and short-term use of NSAIDs as being safe" (*Circulation* 2011;123:2226-2235). One interesting aspect of this study was the use of rofecoxib (Vioxx) prior to its withdrawal in 2004. While rofecoxib was found to increase cardiovascular risk (the reason for its withdrawal from the market), it appeared to be no more dangerous than other commonly used NSAIDs and was apparently safer than diclofenac. ■

NHLBI stops AIM-HIGH trial

Niacin may not be effective in preventing cardiovascular disease. The National Heart Lung and Blood Institute (NHLBI) has prematurely stopped the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) clinical trial 18 months earlier than planned. Analysis of the data found that adding high-dose, extended-release niacin to statin treatment in people with heart and vascular disease did not reduce the risk of cardiovascular events. AIM-HIGH participants had well-controlled low-density lipoprotein levels on a statin, however they were at risk of cardiovascular disease due to previous history of cardiovascular disease and a combination of low high-density lipoprotein (HDL) cholesterol and high triglycerides. During the nearly 3 years of the study, patients who took high-dose, extended-release niacin with a statin had increased HDL cholesterol and lower triglyceride levels compared to those who took a statin alone; however, the combination was not effective at reducing fatal or nonfatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures. There also was a "small and unexplained increase in ischemic stroke rates in the high-dose, extended-release niacin group" that contributed to the decision to halt the trial. Termination of the AIM-HIGH trial was announced by press release from the NHLBI on May 26. ■

FDA actions

The FDA has approved linagliptin for the treatment of type 2 diabetes in adults. The drug is an inhibitor of DPP-4, an enzyme that degrades incretin hormones (GLP-1 and GIP). It is approved for use as a stand-alone therapy or in combination with other drugs for type 2 diabetes including metformin. The approval was based on eight double-blind, placebo-controlled trials of nearly 4000 patients that showed improved blood glucose control compared to placebo. Linagliptin is marketed by Boehringer Ingelheim Pharmaceuticals as Tradjenta.

The FDA has approved rilpivirine, a new non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of adults with HIV-1 infections who are treatment naïve. Rilpivirine is to be used as part of a highly active antiretroviral therapy (HAART). The approval was based on two phase 3 trials of nearly 1400 adults with HIV who were observed for 48 weeks, and an additional 96-week trial in which the drug was compared to efavirenz as part of multidrug combinations. Rilpivirine was found to be comparable to efavirenz with regard to percentage of patients with undetectable HIV viral load. Patients who failed rilpivirine are more likely to develop drug resistance than patients who failed efavirenz. Rilpivirine is marketed by Tibotec Therapeutics as Edurant.

Rosiglitazone (Avandia) remains on the U.S. market, but its days may be numbered. In a new step to restrict use of the drug, the FDA has updated the Risk Evaluation and Mitigation Strategy to include a restricted access in distribution plan. Physicians and patients must enroll in the distribution program in order to receive the drug. Rosiglitazone will no longer be available in commercial pharmacies after mid-November and will only be available by mail order through certified pharmacies. Use of the drug is limited to patients who are currently on rosiglitazone and whose diabetes is not controlled by other treatments and who are unwilling to change to pioglitazone (Actos). ■

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- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
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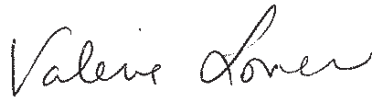

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