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INSIDE

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Tamoxifen Compliance

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a randomly selected population of post-menopausal breast cancer patients treated with either tamoxifen or anastrozole, discordance was found between self-reported adherence to prescribed treatment and actual records of prescription fills provided by local hospital and physician records. The findings support further research in developing strategies to better understand and overcome non-adherence.*

Source: Ziler V, et al. Adherence to adjuvant endocrine therapy in post-menopausal women with breast cancer. *Ann Oncol*. 2009;20:431-436.

Adherence with long-term oral medication for chronic illness is a challenge of increasing importance, particularly as new oral formulations for a variety of cancer types have become available. Certainly, non-adherence is a factor of considerable importance in the explanation of outcomes that are less than desired. In this regard, adjuvant endocrine therapy for early-stage breast cancer is of particular concern because earlier reports have suggested poor adherence to prescribed treatment. For example, previous studies evaluating adherence to tamoxifen (TAM) using self-reported evaluation or database claim methods found adherence rates ranging from 65%-85% at different lengths of follow-up.[1-4]

The current analysis from Marsburg, Germany was designed to evaluate the rate of adherent patients in a randomly selected sample of post-menopausal women with primary breast cancer who had been assigned to an adjuvant endocrine treatment with TAM or anastrozole (ANA). For this, a random sample of 100 post-menopausal women with breast cancer (50 TAM and 50 ANA) who had received surgery for their primary breast cancer in 2004/2005 and, thereafter, had been assigned to an adjuvant endocrine treatment were evaluated. Adherence rate was determined using both a detailed questionnaire and a retrospective prescription check of hospital and physician records. A patient was counted as adherent with a self-reported tablet intake of 80% or more and if a medication possession ratio of 80% or more was achieved.

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Regarding the baseline characteristics, a significant difference in mean age was noticed in women on ANA vs. TAM (65 [± 3 years] and 72 [± 3 years]; $p < 0.001$). All women on TAM and ANA reported themselves to be adherent (100%). After controlling for prescriptions, only 40 (80%) and 27 (69%) of the women on TAM and ANA, respectively, were still classified as adherent ($p < 0.01$ and $p < 0.01$ vs. self-report). There was no significant correlation of adherence to any baseline characteristics or side effects in a logistic regression model.

■ COMMENTARY

An important goal of any therapeutic intervention is to achieve comparable efficacy in routine clinical practice, as demonstrated in randomized clinical trials. However, a similar magnitude of adherence will be necessary in routine clinical practice to assure comparable clinical effects. The current results further support the data on suboptimal adherence of women with breast cancer on adjuvant TAM treatment and indicate comparable findings for adjuvant ANA. Physicians need to be aware of adherence issues to explain, as possible, the importance of compliance if the therapeutic goals are to be achieved, and to be prepared with alternative treatments or strategies if it is clear that patients are not adhering to the current treatment plan. More prospective studies are needed to increase our understanding of the underlying reasons for non-adherence, in general, and in women with breast cancer specifically. ■

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Adjuvant Imatinib for GIST

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a multicenter, randomized, placebo-controlled phase III trial, imatinib (400 mg/d) administered for one year was demonstrated to enhance progression-free survival for patients with gastrointestinal stromal tumors. This study was the basis for the FDA approval for such treatment in this setting.*

Source: DeMatteo RP, et al. Adjuvant imatinib mesylate after resection of localized primary gastrointestinal stromal tumors: a randomised, double blind, placebo-controlled trial. *Lancet*. 2009;373:1097-1104.

PRIOR TO THE INTRODUCTION OF EFFECTIVE TYROSINE kinase inhibitors, the incidence and prevalence of mesenchymal tumors arising within the gastrointestinal tract was neither well-studied nor understood. What was known was that, as a group, such tumors were particularly aggressive with recurrence- and disease-related death rates, approximating 50% despite surgical resection.[1,2] With the demonstration of the tyrosine kinase receptor (KIT) within gastrointestinal stromal tumor (GIST) cells[3] and the discovery that gain-of-function mutations in the KIT gene are important in the pathogenesis of GIST,[4-6] the introduction of targeted inhibition of that gene by imatinib has resulted in a remarkable transformation in the medical approach to this disease.[5-7]

With the demonstration of the effectiveness and safety of imatinib treatment for patients with metastatic GIST, the question of whether adjuvant treatment after initial surgical resection would be associated with reduced rates of recurrence and improved overall survival was raised. To address this, DeMatteo et al representing the American College of Surgeons Oncology Group (ACOSOG) Inter-

group Adjuvant GIST Study Team undertook a randomized, phase III, double-blind, placebo-controlled, multicenter trial. To be eligible, adult patients treated at any of the 230 participating institutions had to have complete gross resection of a primary gastrointestinal stromal tumor of at least 3 cm in size which was immunohistochemically positive for the KIT protein. Patients were randomly assigned to imatinib 400 mg (n = 359) or placebo (n = 354) daily for one year after surgical resection. Patients and investigators were blinded to the treatment. Patients assigned to placebo were eligible to crossover to imatinib treatment in the event of tumor recurrence. The primary endpoint was recurrence-free survival, and analysis was by intention to treat. Accrual was stopped early because the trial results crossed the interim analysis efficacy boundary for recurrence-free survival.

All randomized patients were included in the analysis. At median follow-up of 19.7 months (minimum-maximum 0-56.4), 30 (8%) patients in the imatinib group and 70 (20%) in the placebo group had tumor recurrence or died. Imatinib significantly improved recurrence-free survival compared with placebo (98% [95% CI 96-100] vs. 83% [78-88] at one year; hazard ratio [HR] 0.35 [0.22-0.53]; one-sided $p < 0.0001$). Adjuvant imatinib was well tolerated, with the most common serious events being dermatitis (11 [3%] vs. 0), abdominal pain (12 [3%] vs. six [1%]), and diarrhea (ten [2%] vs. five [1%]) in the imatinib group and hyperglycemia (two [< 1%] vs. seven [2%]) in the placebo group.

■ COMMENTARY

This was a randomized, double-blind study of imatinib for patients with GIST at high risk for recurrence after resection. To recap, after 18 months of median follow-up, progression-free survival (PFS) was 97% in the imatinib group vs. 83% in the placebo group. The improvement in PFS was seen across a broad range of tumor sizes. The findings were sufficiently impressive both to warrant early termination of the study based upon demonstrated efficacy and to persuade the FDA to approve imatinib for use in the adjuvant setting for KIT-positive GIST patients.

It is very important for patients with GIST tumors to be correctly identified at the time of initial resection, so that the benefit of adjuvant therapy is not potentially missed. Resected tumors should be tested for the presence of the KIT tyrosine kinase receptor (CD117 stain); however, there have been reports of CD117-negative GISTs. Platelet-derived growth-factor receptor (PDGFR) staining may also prove helpful. Molecular genetic analysis of c-kit and PDGFR may not only help to identify patients with GIST but, because certain mutations in these genes are associated with imatinib resistance, testing may serve to help assess the potential benefit of therapy, as other drugs have been developed that have activity in imatinib-resistant forms of GIST.[8]

The duration of imatinib therapy continues to be in question. It is notable that six months after completion of adjuvant therapy, recurrences began to increase, raising the question of whether a more prolonged treatment would be associated with even greater PFS. To this end, the European Organization for Research and Treatment of Cancer (EORTC) trial 62024 is testing zero vs. two years of adjuvant imatinib and the Scandinavian Sarcoma Group trial XVIII is testing one vs. three years of treatment.

For now, there is good evidence that one year of adjuvant imatinib therapy is both safe and effective in reducing GIST recurrence. Just how long beyond that year remains unknown, and because the drug is not without some toxicity, and keeping in mind the issue of acquired resistance to this agent, medical oncologists will need to wait for the maturation of current studies before being confident that longer adjuvant treatment is in the patient's best interest. ■

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Time-to-Progression after Chemotherapy Increased in Unmutated IgVh CLL

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

Division of Hematology/Oncology, University of Chicago

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

Synopsis: *Unmutated immunoglobulin variable heavy chain (IgVh) in patients with chronic lymphocytic leukemia is associated with worse outcome. Lin et al explored the role of IgVh mutational status on outcome after fludarabine, cyclophosphamide, and rituximab for CLL in 177 patients. They found that complete remission rates were similar at 73% and 83% for unmutated and mutated IgVh, respectively (*p = *0.12). Among those achieving CR, time-to-progression was considerably shorter for unmutated IgVh (*p < *0.001) and the results were maintained after adjustment. Survival was not different by mutational status after adjustment. Unmutated IgVh in CLL is associated with more rapid disease progression after CR.*

Source: Lin K, et al. Relevance of the immunoglobulin VH somatic mutation status in patients with chronic lymphocytic leukemia treated with fludarabine, cyclophosphamide, and rituximab (FCR) or related chemoimmunotherapy regimens. *Blood*. 2009;113:3168-3171.

Chronic lymphocytic leukemia (CLL) is a common lymphoproliferative disorder. As with most cancers, the disease is highly heterogeneous, with extremely varied survival. Somatic mutations in the immunoglobulin variable heavy chain (IgVh) has been described in around 50% of CLL patients,[1,2] and are of considerable prognostic importance. For patients with CLL cells that use unmutated IgVh, survival is poor relative to patients having CLL cells using mutated IgVh. Whether this higher mortality relates to lower response to induction, higher relapse or both is not clear.

Investigators from MD Anderson Cancer Center evaluated the pre-treatment IgVh mutational status from samples of 177 CLL patients treated with fludarabine, cyclophosphamide, and rituximab (FCR). In some patients, the treatment protocol employed FCR augmented by higher doses of rituximab, mitoxantrone, or alemtuzumab. Mutated IgVh was defined as detecting greater than 2% mutations (< 98% homology to germline status).

Mutational status showed 59% having unmutated IgVh and 41% having mutated IgVh. As expected, unmutated IgVH was associated with higher white blood cell count at treatment, elevated beta-2-microglobulin, and abnormal karyotype. Restricting results to FCR-only patients, complete remission (CR) rate was 73% for unmutated and 83% for mutated CLL ($p = 0.12$), respectively. Flow-cytometry negative CR rates were 57% for unmutated and 67% for mutated ($p = 0.21$), respectively. Protocols with FCR as a base protocol and incorporating other treatment showed similar trends with a marginal trend of lower initial CR ($p = 0.46$).

Time-to-progression (TTP) among those who achieved CR was inferior for unmutated IgVh compared to mutated at 47% vs. 82%, respectively ($p < 0.001$). The results were maintained when only considering those with a flow-cytometry negative CR. In a multivariate analysis, only unmutated IgVh status was strongly associated with TTP (HR = 3.8, $p < 0.001$), whereas standard factors such as older age, elevated beta-2 microglobulin, cytogenetic abnormalities, elevated white blood cell count, CD38 positivity, and time interval before treatment were not statistically significant.

Six-year overall survival was 71% in CLL patients having an unmutated IgVh compared to 82% in those without such a mutation ($p = 0.05$). In multivariate analysis, unmutated status was no longer significant, whereas older age and higher beta-2 microglobulin did predict for worse survival.

■ COMMENTARY

Because of the heterogonous nature of CLL, the optimal timing for treatment and regimen remain controversial and must be individualized. Somatic mutations in the immunoglobulin variable heavy chain (IgVh) have emerged as an adverse prognostic factor that can be identified in around half of the patients. Poor prognostic biologic factors can impair outcome through resistance to therapy, higher risk of relapse once remission is attained, or a combination of both. Lin et al suggest in this study that the adverse influence of unmutated IgVh is primarily attributable to disease relapse rather than low remission rates. Specifically, among patients who received the FCR regimen, complete remission rates were not statistically different by mutational status, whereas time-to-progression after complete remission was much shorter among patients having unmutated IgVh. The shorter time-to-progression was confirmed in multivariate analysis. Lin et al suggest that more aggressive remission strategies be considered in CLL patients harboring unmutated IgVh.

The data provided herein are particularly useful in demonstrating the prognostic relevance of IgVh after FCR,

an aggressive regimen often used for younger patients where the goal is optimal and prolonged disease control. Still, the findings should be considered preliminary rather than confirmatory, and the conclusions may be premature. First, the remission rates, although statistically similar, were 10% lower in absolute terms in patients with unmutated IgVh. If this difference is true, it would be significant in a larger cohort, and suggests both remission rates and relapse after remission are influenced by IgVh mutational status. Second, overall survival was lower for unmutated IgVh in univariate analysis, but not after adjusting for other factors. It would be difficult to attribute the lack of a survival difference to only an inadequately powered sample since time-to-progression was markedly worse in the unmutated patients. Even though TTP was shorter with unmutated disease, these data raise an intriguing hypothesis that FCR mitigated part of the adverse influence of unmutated IgVh.

While IgVh mutational status may become clinically useful, we need considerably more data before we can make treatment decisions, such as more intensive consolidation, based on this test, such as more intensive consolidation. While higher stage still is the most widely used clinically tool to determine prognosis and treatment, a dizzying array of novel prognostic markers have been studied for CLL. A non-inclusive list includes lymphocyte doubling time, CD38 positivity, zeta chain associated protein 70 (ZAP 70), karyotypic abnormalities, bone marrow histology, and beta-2 microglobulin, as well as IgVh mutational status. Unmutated IgVh appears to be a strong adverse prognostic factor in most studies.[1,2] Still, the optimal prognostic marker remains unknown, and some markers, such as ZAP-70, may be better or additive to IgVh.[3] Most likely, a panel of markers will be needed to supplement clinical information such as stage, age, and health status.

Technical issues also warrant discussion. Assessing IgVh is technically difficult and not clinically available. Further, a gold-standard definition for unmutated status is lacking, although recent studies suggest > 97% sequence homology to the somatic genotype should define unmutated IgVH.[4] In this study, > 98% sequence homology was used to defined unmutated.

In conclusion, mutated IgVh among CLL patients treated with FCR was associated with a shorter time-to-progression after remission. Further studies will be needed to determine whether treatment decisions should be influenced by IgVh mutational status. ■

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Gefatinib (Iressa) as First-line Therapy for Advanced NSCLC in Patients with Poor Performance

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a phase II trial of gefitinib for patients with advanced NSCLC, demonstrable EGFR mutation, and poor performance status (PS 2-4), Inoue et al report a median survival of 17.8 months. In addition to a high-response and disease-control rates (66% and 90%, respectively), improvement in performance status was observed in 78% of the patients.*

Source: Inoue A, et al. First-line gefitinib for patients with advanced non-small cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. *J Clin Oncol*. 2009;27:1394-1400.

THE PERCENTAGE OF PATIENTS WITH NEWLY DIAGNOSED non-small-cell lung cancer (NSCLC) who present with poor performance status is remarkably high, perhaps reflecting advanced age, existing comorbidities, and/or the functional impact of this malignancy. For example, from a series of more than 500 patients with NSCLC, Lilenbaum et al found that the prevalence of poor performance status (Eastern Cooperative Oncology Group [ECOG] PS 2 to 4) was 34% when estimated by practitioners and 48% when determined by patients themselves.[1] This is indeed of relevance because the optimal treatment for advanced stage patients with PS2 is quite controversial[2-5] and there remains a prevalent sense that for those with PS3 or PS4, treatment beyond supportive care is of no value.[6]

Gefitinib (Iressa; AstraZeneca), an orally active, epidermal growth-factor receptor (EGFR) tyrosine-kinase inhibitor (TKI), has shown novel antitumor activity in patients with advanced NSCLC.[7,8] Because the toxicity of gefitinib is less than that of cytotoxic agents, its utility as first-line treatment for patients with NSCLC having poor PS was addressed by Inoue et al from Japan. An earlier study, also from Japan, suggested that gefitinib should not be used in unselected, poor-performance NSCLC patients due to its low efficacy and toxicity (particularly in the development of interstitial lung disease).[9] However, Inoue et al developed a method[10] enabling them to determine EGFR mutation status and, thereby, select individuals with the greatest likelihood of responding to TKI therapy.

Thus, the current multicenter, phase II study was undertaken to investigate the efficacy and feasibility of gefitinib for patients with advanced NSCLC harboring EGFR mutations without indication for chemotherapy as a result of poor PS. For this, chemotherapy-naïve patients with poor PS (patients 20 to 74 years of age with ECOG PS 3 to 4, 75 to 79 years of age with PS 2 to 4, and > 80 years of age with PS 1 to 4) who had EGFR mutations were enrolled and received gefitinib (250 mg/d) alone.

Between February 2006 and May 2007, 30 patients with NSCLC and poor PS, including 22 patients with PS 3-4, were enrolled. The overall response rate was 66% (90% CI, 51% to 80%), and the disease control rate was 90%. PS improvement rate was 79% ($p < .00005$); in particular, 68% of the 22 patients improved from > PS 3 at baseline to < PS 1. The median progression-free survival, median survival time, and one-year survival rate were 6.5 months, 17.8 months, and 63%, respectively. No treatment-related deaths were observed. It was notable that a clinically valuable improvement in performance status was evident in the majority of treated patients and that EGFR mutations were observed in a diverse group of NSCLC patients, not necessarily female, non-smokers with adenocarcinoma histology.

■ COMMENTARY

These are exceptionally positive results considering the dismal prognosis experienced by poor PS NSCLC patients treated with chemotherapy or supportive care. The question, of course, is just how applicable they will be to the population of patients in the United States or Europe. In Japan, EGFR mutations are found in up to 40% of NSCLC cases, whereas in the United States, the rate is more like 10%. Nonetheless, the findings would support an effort to determine EGFR status in all patients with advanced NSCLC and a trial to assess whether similar results could be observed in that segment of the overall NSCLC patients, especially those with poor PS. ■

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Bisphosphonates and Breast Cancer: Good News and Bad News

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Two recent reports relate to the expanded use of zoledronic acid or other bisphosphonate in current oncologic practice. A report of a randomized, clinical trial demonstrated a small but clear benefit of a combination of endocrine therapy with zoledronic acid compared to endocrine therapy alone for early-stage, hormone-responsive breast cancer patients. In a separate article, the prevalence of the untoward bisphosphonate treatment-related osteonecrosis of the jaw was estimated to be approximately 5% in patients with advanced breast cancer. Interestingly, osteonecrosis of the jaw was not observed in the larger randomized trial in which early-stage breast cancer patients were enrolled.*

Sources: Gnant M, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med*. 2009; 360:679-691; Walter C, et al. Incidence of bisphosphonate-associated osteonecrosis of the jaws in breast cancer patients. *Cancer*. 2009;115:1631-1637.

SKELETAL METASTASES REMAIN THE MOST COMMON SITE of distant metastases in breast cancer patients. There is now expanding literature on the potential antineoplastic effect of certain bisphosphonates[1,2] which strengthen the rationale for the inclusion of such an agent in early management of this disease. In recent issues of the *New England Journal of Medicine* and *Cancer*, we learned of a clinical demonstration of such a salutary effect, but are reminded of one important concern, that of osteonecrosis of the jaw.

Gnant et al, representing the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12), examined the effect of adding zoledronic acid to a combination of either goserelin and tamoxifen or goserelin and anastrozole in premenopausal women with endocrine-responsive early breast cancer. For this, 1,803 patients were randomly assigned to receive goserelin (3.6 mg subcutaneously every 28 days) plus tamoxifen (20 mg/day given orally) or anastrozole (1 mg/day given orally) with or without zoledronic acid (4 mg given intravenously every six months) for three years. The primary endpoint was disease-free survival; recurrence-free survival and overall survival were secondary endpoints.

After a median follow-up of 47.8 months, the disease-free survival (DFS) rate for those who received tamoxifen was 92.8%, compared with 92% for those who received anastrozole. For those who received endocrine therapy alone, the DFS was 90.8%, whereas for those who received zoledronic acid plus endocrine therapy, DFS was 94.0%. Thus, there was no significant difference in DFS between the anastrozole and tamoxifen groups (hazard ratio for disease progression in the anastrozole group, 1.10; 95% confidence interval [CI], 0.78 to 1.53; $p = 0.59$). Nonetheless, the addition of zoledronic acid to endocrine therapy, as compared with endocrine therapy without zoledronic acid, resulted in an absolute reduction of 3.2% and a relative reduction of 36% in the risk of disease progression (hazard ratio, 0.64; 95% CI, 0.46 to 0.91; $p = 0.01$). However, the addition of zoledronic acid did not significantly reduce the risk of death (hazard ratio, 0.60; 95% CI, 0.32 to 1.11; $p = 0.11$).

In this trial, the addition of zoledronic acid was not associated with significant adverse events. Patients receiving anastrozole experienced more arthralgias and bone discomfort than those receiving tamoxifen and, in both groups, these symptoms increased for those receiving zoledronic acid. It was notable, however, that none of the 1,803 patients were found to have suffered osteonecrosis of the jaw.

In this light, the article published in *Cancer* by Walter et al was of interest. They performed a retrospective analysis of metastatic breast cancer patients treated with bisphosphonates at the breast unit of the Dr. Horst Schmidt hospital in Wiesbaden, Germany from January of 2000 to March of 2006. All patients were contacted, and missing data were completed through structured interviews with their dentists and physicians (n = 75). Primary outcome was the development of bisphosphonate-associated osteonecrosis of the jaw and the detection of possible additional trigger factors for the development of this untoward outcome.

Of the 117 patients who fulfilled the inclusion criteria, information was available for 75 who were still living. Of these, four patients had developed ONJ, resulting in a prevalence of 5.3%. Of these, three patients received zoledronate only and one patient had pamidronate followed by zoledronate and ibandronate. A tooth extraction could be identified as an additional trigger factor for two patients.

■ COMMENTARY

These papers highlight the rapidly developing interest and concern regarding zoledronic acid and other drugs in this class amongst oncologists. These drugs are known to inhibit bone resorption due to their direct cytotoxic effect on osteoclasts.[3,4] Whether that mechanism alone is sufficient to account for the previously reported reduction in bone metastases[5] or the improvement in DFS found in the current study, is a point of conjecture. Certainly, other effects, such as that on angiogenesis[2] or on anti-tumor immune responses could be equally relevant.[6,7]

The similar rates of disease-free survival found by Gnant et al comparing anastrozole with tamoxifen for early-stage breast cancer in premenopausal women is notable in light of the superiority of aromatase inhibitors over tamoxifen in post-menopausal patients.[8,9] As Gnant et al suggest, this may relate to the dominant effect of ovarian suppression on estrogen and androgen levels in premenopausal women, limiting the availability of substrate for aromatase activity.

These data from a large, randomized, multicenter trial clearly demonstrate a small but significant improvement in DFS by the addition of zoledronic acid to adjuvant endocrine therapy in premenopausal patients with estrogen-responsive early breast cancer. This also has been observed in similarly treated post-menopausal breast cancer patients.[5] The concern over osteonecrosis of the jaw, although not observed among the patients on the clinical trial, remains relevant, occurring in about 5% of cases in the series reported from Germany. Why the occurrence of osteonecrosis of the jaw was not observed in the current trial, or in the earlier trial of post-menopausal women[5] remains conjecture, although it might relate to the more debilitated condition of patients with metastatic disease, such as those included in the German report. ■

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CME Questions

20. Compared with tamoxifen, adherence by post-menopausal breast cancer patients to prescribed anastrozole is:
a. better.
b. about the same.
c. worse.

21. The recommended duration of adjuvant imatinib therapy for patients with resected gastrointestinal stromal tumors is:
a. six months.
b. one year.
c. three years.
d. five years.

22. What outcome was associated with unmutated immunoglobulin variable heavy chain (IgVh) among CLL patients treated with fludarabine, cyclophosphamide, and rituximab?
a. More infectious complications
b. Better overall survival
c. Shorter time-to-progression after remission
d. Higher complete response rates

23. Gefitinib treatment was associated with a 66% response rate and a median survival of 17.8 months in which group of lung cancer patients:
a. Performance Status 0-2, NSCLC
b. Performance Status 2-4, NSCLC
c. Performance Status 0-2, EGFR mutated, NSCLC
d. Performance Status 2-4, EGFR mutated, NSCLC

24. The addition of zoledronic acid to endocrine therapy, as compared with endocrine therapy alone, resulted in an absolute reduction in disease-free survival at 48 months of approximately:
a. 3%.
b. 15%.
c. 36%.
d. 75%.

Answers: 20. (b); 21. (b); 22. (c); 23. (d); 24. (a)

CME Objectives

The objectives of *Clinical Oncology Alert* are:

- to present the latest information regarding diagnosis and treatment of various types of cancer;
- to present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- to describe new advances in the field of oncology.

In Future Issues:

HER-2 Expression and MRI of the Breast

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
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Best management of acute ankle sprain

Source: Lamb SE, et al. Mechanical supports for acute ankle sprain. *Lancet* 2009;375:575-581.

A SEVERE ANKLE SPRAIN (ANK-S) might seem like a minor injury, but clinicians may be underestimating the burden of consequence. In addition to the immediate period of limited mobility, full functional restoration takes between 3-9 months for as many as 70% of affected individuals. Indeed, it is not uncommon to see long-term symptoms referable to the ankle sprain, including recurrent swelling, pain, and limitation of activity. Because ANK-S is a commonplace event, confirming the best approach to initial management merits investigation.

Lamb et al randomized participants presenting to EDs in the United Kingdom with severe ANK-S (n = 584) to 1 of 4 treatments: an Aircast® brace, Bledsoe boot, below-knee cast, or double-layer tubular compression bandage.

Participants generally used treatments short-term, i.e., 10 days, and then PRN. Tubular compression bandage was the least efficacious method at 1, 3, and 9 months and was similar in efficacy to the Bledsoe boot. The below-knee cast was the most effective treatment, but Aircast outcomes were similar for ankle functionality at 3 months. Overall, the below-knee cast showed the best early symptomatic recovery, as well as functional recovery by 3 months. Although the philosophy of early mobilization has achieved some popularity, these data would suggest that tools that limit mobilization early (i.e., cast, Aircast), should be considered preferential. (Note: There is more than one Bledsoe boot; because Bledsoe provides boots with either flexion-extension mobility or full immobilization, it is possible that other versions of the Bledsoe boot might be more efficacious). ■

Metabolic syndrome and salt sensitivity

Source: Chen J, et al. Metabolic syndrome and salt sensitivity of blood pressure in non-diabetic people in China. *Lancet* 2009;373:829-835.

ALTHOUGH DEFINITIONS OF WHAT constitutes metabolic syndrome (MBS) vary, there is general agreement that insulin resistance (IR) is a fundamental component. By leading to sodium retention, IR may contribute to the development of hypertension (HTN).

Blood pressure effects of salt restriction are highly variable, but one would anticipate that MBS subjects might respond more intensely based upon the IR-to-sodium retention link. To investigate this, Chen et al studied 1881 nondiabetic subjects, of whom 283 had MBS. All participants were fed a low-sodium diet (= 3 g NaCl/d) for 7 days, followed by a high-sodium diet (= 18 g NaCl/d) for 7 days. At baseline, the mean BP in the MBS group was 128/81 mm Hg vs 115/72 mm Hg in those without MBS.

High-salt sensitivity was defined as a BP change of 5 mm Hg or more in response to dietary salt modulation. At the end of each diet period, MBS subjects had a threefold or greater odds ratio for high-salt sensitivity (both to a rise in BP with sodium load, as well as a reduction in BP with sodium restriction). The benefits of salt restriction in persons with MBS may be more substantial than the general population. ■

Oseltamivir-resistant influenza

Source: Dharan NJ, et al. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA* 2009;301:1034-1041.

PROGRESSIVE RESISTANCE OF INFLUENza A virus (FLU-A) to adamantanes (i.e., amantadine, rimantadine) led to the 2006 CDC recommendation against their use. Initial resistance patterns of next-generation pharmacotherapies for FLU-A, the neuraminidase inhibitors (i.e., oseltamivir, zanamivir), were very reassuring. Recently, growing resistance patterns to oseltamivir (OSTV) are shaping revised CDC recommendations.

Volunteer clinicians around the United States, known as sentinel physicians, monitor patients who present with influenza-like illness and send samples to the CDC for confirmation of influenza virus status. Among FLU-A viruses assessed in the 2007-2008 influenza season, only 12.3% were OSTV-resistant. Comparison of the demographics of subjects with OSTV-resistant FLU-A to subjects with non-resistant profiles did not provide any insight into particular at-risk groups (or protected groups), including age, geography, symptoms, etc.

OSTV resistance profiles changed dramatically in the FLU-A samples from Sept. 28, 2008, to Feb. 19, 2009: 98.5% of H1N1 FLU-A samples (264/268) were OSTV-resistant! Experts are uncertain about the mechanism by which OSTV resistance has proliferated.

Current options in an environment of high OSTV resistance include zanamivir, or OSTV plus rimantadine. ■

Low back radiology: Roadmap or mirage?

Source: Chou R, et al. Imaging strategies for low-back pain. *Lancet* 2009;373:463-472.

LOW BACK PAIN (LBP) IS RESPONSIBLE for as much as one-third of all disability dollars spent in the United States. When patients present with acute LBP, clinicians are tempted to perform radiographic studies (MRI, CT, plain films) to try to identify the source of the symptomatology. Unfortunately, the preponderance of current evidence suggests that findings commonly reported on radiographic studies such as narrowed disk space, loss of lumbar lordosis, and osteoarthritic changes, are just as common in asymptomatic volunteers as in symptomatic LBP sufferers.

Chou et al performed a meta-analysis of clinical trials which enrolled patients and included immediate imaging (CT, MRI, or plain films) and compared them with trials of similar patients who did not undergo imaging (total n = 1804). In addition to reporting radiography utilization, included trials had to provide information on outcomes of pain or function, quality of life, mental health, overall improvement, and patient satisfaction.

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Chou et al found that in the absence of signs of a serious underlying condition (e.g., fever, weight loss, history of cancer), immediate imaging was not associated with improved outcomes. Indicative of the need for more public education, the article also reminds us that in one study, patient preference to undergo radiography was as high as 80%.

Routine radiography for acute LBP does not improve outcomes, is associated with substantial cost, and may suggest pathology which is, in effect, unrelated to the symptomatology. ■

Bariatric surgery and reversal of dysglycemia

Source: Salinari S, et al. First-phase insulin secretion restoration and differential response to glucose load depending on the route of administration in type 2 diabetic subjects after bariatric surgery. *Diabetes Care* 2009;32:375-380.

MOST TYPE 2 DIABETICS (DM2) WHO undergo bariatric surgery enjoy a prompt reversal—or at least a substantial diminution—of their dysglycemia. These salutary effects occur both after malabsorptive surgery (diverting the digestive tract around to bypass components of the small intestine) or restrictive surgery (diminishing gastric capacity). The mechanisms by which surgery improves glucose regulation appear to go beyond simple weight loss; indeed, glucose regulation improves well before meaningful weight loss has occurred, suggesting that some change in intestinal glucose modulation factors must be involved.

Salinari et al studied glucose metabolism in 9 DM2 subjects who underwent biliopancreatic diversion bariatric surgery, comparing their glucose metabolism with healthy, normal-weight controls.

The healthy pancreas provides a bolus of preformed insulin immediately in response to mealtime increases in plasma glucose. One of earliest manifestations of DM2 is loss of first-phase insulin secretion, leading to a consistent mismanagement of glucose, since early elevations of plasma glucose are not met with a prompt matching insulin bolus. In this trial, the first-phase insulin response was restored by 1 month after surgery. Similarly, beta-cell responsiveness to glucose elevation was normalized; and lastly, insulin sensitivity was restored to essentially normal. Concordant with the concept that elimination of some intestinal component is central to these phenomena, sensitivity to oral glucose was improved to a greater degree than was intravenous glucose. Incretin levels (GLP, GIP), however, were unchanged.

Malabsorptive bariatric surgery provides prompt regression of DM2, apparently due (at least in part) to some as yet unidentified intestinal hormone, and independent of identified incretin hormones such as GLP and GIP. ■

Herpes zoster in TNF-treated RA patients

Source: Strangfeld A, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-α agents. *JAMA* 2009;301:737-744.

THE EVOLUTION OF PHARMACOTHERAPY for rheumatoid arthritis (RA) has led to the development of agents which, at least, offer major symptomatic improvement, and at best, promise remission. Because TNF agents involve modulation of steps critical to immune integrity, vigilance for serious bacterial infections is required. Yet, whether TNF agents impact the incidence of viral infections, which is also important, has been little-studied. Population studies on patients with RA have demonstrated a doubling of risk for herpes zoster compared to a control population.

Strangfeld et al enrolled RA patients (n = 5040) receiving either TNF agents or conventional DMARDS, such as methotrexate. Herpes zoster incidence was monitored over 36 months.

Overall, TNF agents were associated with an increased zoster incidence (hazard ratio = 1.82) compared to conventional treatment. Among the TNF agents, there was a distinct difference between etanercept, which did not show a statistically significant increase in zoster risk, vs infliximab and adalimumab, which did. The authors suggest that patients treated with the latter two agents merit particular vigilance for early signs and symptoms of herpes zoster to allow prompt intervention. ■

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*.

FDA Warning: Pharmaceuticals in "Natural" Products

In this issue: Aspirin dose and cardioprotection; uncovering modafinil's abuse potential; proton-pump inhibitors and clopidogrel; FDA actions.

Finding pharmaceuticals in natural products

Some natural products are not so "natural" after all. The FDA has warned consumers for several months that a number of weight-loss products contain undeclared pharmaceutical ingredients. The newest products to join the list are Herbal Xenicol which contains cetilistat (a drug similar to orlistat that is not approved in this country), as well as Slimbionic and Xsvelten, both of which contain sibutramine (the prescription medication also known as Meridia®). The FDA's list of over-the-counter weight-loss agents that contain undeclared active pharmaceutical ingredients now includes 72 products. Some of the other undeclared pharmaceutical ingredients found in these products include fenproporex (an amphetamine derivative no longer available in this country), fluoxetine (Prozac®, an SSRI), furosemide (Lasix®, a loop diuretic), and even phenytoin (Dilantin®, an antiseizure medication). The FDA is seeking recalls on many of these products; however, some are available only online and previous recall efforts have proved inadequate.

In a related story, the FDA has announced a voluntary recall of Zencore Plus, the heavily marketed product for "natural male enhancement," which has been found to contain benzamidenafil, a new PDE5 inhibitor not yet available in this country. Benzamidenafil is similar in action to sildenafil (Viagra®) and tadalafil (Cialis®). PDE5 inhibitors are noted to have a drug interaction with nitrates, leading to potential life-threatening risk of sudden and profound drop in blood pressure. Zencore Plus is distributed by Hi-Tech Pharmaceuticals in Norcross, GA, and is widely sold in health food stores, by mail order, and by Internet sales.

Aspirin dose and cardioprotection

What is the best dose of aspirin for patients taking dual therapy with clopidogrel to prevent cardiovascular events? Investigators looked at 15,595 patients with cardiovascular disease or multiple risk factors in an observational analysis from a double-blind, placebo-controlled randomized trial. Patients were randomized to doses of aspirin less than 100 mg (75 mg or 81 mg), 100 mg, or greater than 100 mg (150 mg or 162 mg) with or without clopidogrel. The primary efficacy outcome was the composite of myocardial infarction, stroke, or cardiovascular death and the primary safety endpoint was severe life-threatening bleeding. In patients given aspirin alone, the hazard ratio for the efficacy and safety endpoints were the same regardless of aspirin dose. In patients given aspirin with clopidogrel, there was a statistically nonsignificant associated reduction in efficacy with aspirin doses over 100 mg, and a

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

significantly higher increase in harm (hazard ratio, 1.30 with clopidogrel plus aspirin greater than 100 mg). The authors conclude that daily doses of aspirin greater than 100 mg were not associated with benefit and may be associated with harm in patients also taking clopidogrel. Therefore, daily doses of aspirin 75-81 mg optimize efficacy and safety in patients requiring long-term aspirin therapy, especially in patients receiving dual antiplatelet therapy (*Ann Intern Med* 2009;150:379-386). This is especially important given the recent U.S. Preventive Services Task Force recommendation that encourages men ages 45-79 years to take aspirin preventively when the potential benefit of a reduction of myocardial infarction outweighs the potential harm of an increase in gastrointestinal hemorrhage. Women ages 55-79 years are also encouraged to use aspirin when the potential benefit of a reduction in ischemic stroke outweighs the potential harm of increased gastrointestinal hemorrhage (*Ann Intern Med* 2009;150:396-404).

PPIs and clopidogrel

Increasing evidence suggests that proton pump inhibitors (PPIs) may attenuate the effect of clopidogrel on platelet aggregation. PPIs are often used prophylactically in patients with acute coronary syndrome (ACS), as patients on clopidogrel and aspirin may be at higher risk for GI bleeding. A new study from VA researchers was set up to determine if there are clinical implications from the interaction between PPIs and clopidogrel.

In a retrospective cohort study of 8205 patients with ACS taking clopidogrel, 63.9% were also prescribed a PPI at discharge, during follow-up, or both. Death or rehospitalization for ACS occurred in 20.8% of patients taking clopidogrel without a PPI and 29.8% patients taking clopidogrel with a PPI. Use of clopidogrel plus a PPI was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel without a PPI (adjusted odds ratio, 1.25; 95% confidence interval, 1.11-1.41). Patients taking a combination of the two drugs were at higher risk for hospitalizations for ACS and revascularization procedures, but not for all-cause mortality. Patients taking a PPI without clopidogrel were not at higher risk for rehospitalization. The authors conclude that concomitant use of clopidogrel and a PPI after hospital discharge for ACS is associated with an increase risk of adverse outcomes, suggesting that PPIs may attenuate the benefits of clopidogrel, and that PPIs should only be used with clopidogrel if there is a clear indication, and not for routine prophylaxis (*JAMA* 2009;301:937-944).

Modafinil's abuse potential

Modafinil (Provigil®) is a wake-promoting medication used to treat narcolepsy and other sleep disorders. Recently, the drug has be used off-label to enhance cognition in psychiatric patients and even in healthy patients seeking a memory boost. Modafinil has been touted as having a low abuse potential; however, a new study questions that assumption. Most stimulant medications, such as methylphenidate and amphetamine, increase brain dopamine levels. Modafinil was thought to exert its effect in the brain on pathways other than dopamine, but now there is evidence that dopamine is involved. Researchers from the National Institute on Drug Abuse looked at 10 healthy male volunteers to measure the effects of modafinil at therapeutic dosing of 200 mg and 400 mg given orally. PET scans were used to measure the effect of modafinil on extracellular dopamine and dopamine transporters. Modafinil increased extracellular dopamine and showed evidence of occupancy of dopamine transporters, effects similar to drugs with the potential for abuse. The authors conclude that, considering the increasing use of modafinil, there needs to be heightened awareness for potential abuse of and dependence on modafinil in vulnerable populations (*JAMA* 2009;301:1148-1154).

FDA Actions

The FDA is requiring the manufacturers of metoclopramide (Reglan®) include a boxed warning on their labeling regarding the risk of long-term or high-dose use and tardive dyskinesia. Manufacturers will also be required to implement a risk evaluation and medication strategy (REMS) to ensure patients are provided with a medication guide that discusses the risk. Metoclopramide is approved for the treatment of gastric motility problems associated with GERD, diabetic gastroparesis, and nausea and vomiting.

A new proton pump inhibitor has been approved by the FDA, bringing the number of PPIs on the market to six. Dexlansoprazole is the purified active isomer of lansoprazole (Pepcid®). The drug has a delayed-release formulation designed to provide two separate releases of the medication. It is approved for the treatment of GERD and erosive esophagitis. Takeda Pharmaceuticals will market dexlansoprazole as Kapidex™. ■