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RAPID REVIEW

Expanding Role for Arsenic Trioxide (ATO) in the Treatment of Acute Promyelocytic Leukemia

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

Although the combination of ATRA with anthracyclines has remarkable activity against low-risk APL (WBC < 5,000 and platelets > 20,000) (OS of 80%-90%), it is less active in patients with high-risk disease. Furthermore, there are long-term toxicities associated with the use of anthracyclines, including second malignancies (e.g., MDS and acute leukemia) and dilated cardiomyopathy.

During the past decade, ATO has been shown to be effective in inducing remission in patients with relapsed and newly diagnosed AML.[1,2] ATO is now accepted as the single-most active agent in APL. ATO exerts dose-dependent effects on APL cells with low doses, inducing differentiation and higher doses, causing apoptosis.

Both ATRA and ATO induce the degradation of the PML-RAR fusion protein, providing a rational basis for targeted therapy in APL and possible synergy between these agents. Molecular studies indicate that ATRA targets the RARα domain and ATO targets the PML domains of the fusion protein.[3,4] ATRA increases ATO uptake by leukemia cells through transcriptional upregulation of aquaglyceroporin 9.[5] In-vitro studies demonstrate a synergistic interaction

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between ATRA and ATO and enhanced activity in xenograft models.[6]

Important clinical and basic-science questions include: 1) How best to use ATO in a way that will mitigate toxicity in patients with low- and intermediate-risk disease; 2) How to incorporate ATO into regimens with that will lead to higher OS in high-risk disease; and 3) To understand the molecular mechanisms of ATO activity in APL. This review will first discuss recent clinical trials incorporating ATO into APL treatment regimens, and then discuss new data suggesting the mechanism by which ATO directly targets the PML-RARa gene product, leading to the cure of APL.

CLINICAL TRIALS INCORPORATING ATO INTO APL TREATMENT REGIMENS

The Chinese group[7] treated 61 newly diagnosed APL patients with ATRA induction as a single agent (25 mg/m^2) unless there was a high WBC, in which case, hydroxyurea or idarubicin + Ara-C (100 mg/m^2 for 3-5 days) was added. Patients in CR received consolidation with three regimens: 1) Daunorubicin + Ara-C (7+3); 2) Ara-C pulse (2.5 g/m^2 for 3 days); 3) Ara-C infusion (100 mg/m^2 for 7 days). Finally, patients in CR were randomized to maintenance with: Group 1: ATRA 25 mg/m^2 for 30 days + either 6-MP 100 mg/d x 30d or 15 mg MTX per week x4; Group 2: ATO 0.16 mg/kg/d for 30 days + either 6-MP or MTX; or Group 3: ATRA for 30 days, then ATO for 30 days, then either 6-MP or MTX. They were given five cycles of maintenance. After a median of 18 months, all 20 patients receiving ATRA + ATO maintenance (Group 3) were in CR, while seven of 37 cases on monotherapy maintenance (Groups 1, 2) had relapsed, suggesting a benefit by the addition of ATO. Beginning in 2005, this group treated the next 85 APL patients using the combined ATRA+ATO maintenance regimen. Eighty patients entered CR (94%), with a DFS of 95% and OS of 97% at 5 years. Five patients died within 15 days of induction (three intracranial hemorrhages, one DIC, one retinoic acid syndrome). Importantly, the clinical outcome, when using this regimen, was not influenced by the initial WBC count or FLT3 mutation status.

Ravandi et al treated 82 newly diagnosed APL patients with ATRA + ATO.[8] Patients with WBC > 10,000 also received gemtuzumab ozogamicin (GO) on day 1. The CR rate was 92%. Seven patients died in the first week of treatment. The three-year OS was 85%. One hundred-eleven patients were treated with ATRA + ATO for induction and consolidation (no cytotoxic chemotherapy), with a CR rate of 86% and a three-year RFS rate of 93%.[9] Some hepatotoxicity occurred due to the addition of ATO during induction, but this decreased during consolidation.

In a very important recent study,[10] 72 patients were treated with single-agent ATO used for induction, consolidation, and maintenance (patients received no ATRA or cytotoxic chemotherapy). ATO was given daily for up to 60 days for remission induction; after one month, two courses of consolidation with four weeks ATO were given. Maintenance was 10 days of ATO per month for six months. This study included pediatric patients; only five patients were older than 55. Of the 22 patients with low-risk disease (defined as WBC < 5,000, platelets > 20,000), there was an OS at five years of 100%. High-risk patients had an EFS of only 70% (in part due to seven patients who died during induction from intra-cranial hemorrhage), supporting the addition of ATRA (and perhaps chemotherapy) to ATO in this group. Thirty-three percent of patients had FLT3 mutation, and 23% had an additional cytogenetic change with no effect on clinical outcome.[11] This study could set a new standard of care for patients with low-risk disease that would eliminate anthracyclines, Ara-C, and maintenance cytotoxic therapy, thus preventing the grave long-term consequences that can occur with these agents. However, these data must be confirmed in future studies using patient populations that more clearly represent those treated by adult oncologists. Furthermore, the optimal treatment for patients with high-risk disease remains to be determined, but will certainly include both ATRA and ATO, with the likely addition of some (hopefully low) dose of anthracyclines (or gemtuzumab ozogamicin).

MOLECULAR MECHANISMS

Recent studies have shed light on the molecular mechanisms for the clinical efficacy of ATO. Both PML and the PML-RARα fusion protein contain a zinc-finger motif whose sulfhydryl residues are covalent targets of ATO binding.[12] This induces a conformal change that induced the multimerization of PML and PML-RARα homodimers and heterodimers, which targets them for modification with SUMO moieties by the E3 ligase UBC9. SUMO, like its molecular relative ubiquitin, targets proteins to specific intracellular localizations, and sometimes for degradation, which is the case here. Therefore, by directly binding to PML, ATO promotes the degradation of PML-RARα in an analogous way that ATRA targets the RARα domain of the fusion protein, enhancing its degradation. Hence, the combination of ATRA and ATO provide a pharmaceutical one-two punch whose combined pharmacodynamic endpoint is the destruction of PML-RARα, leading to leukemia cell differentiation or apoptosis.

Clinical data outlined above suggest that single-agent ATO can cure low-risk APL. In other subtypes of AML, attaining a CR leads to cure in only 25%-30% of patients, and only after multiple cycles of high-dose, multi-agent chemotherapy. Relapse from the minimal residual disease state is thought to be due to the resistance of leukemia stem cells (or leukemia initiating cells, LIC) to chemotherapy due to low cell-cycling percentages, abundant ABC-transporter proteins, etc. Why is the situation with ATO in APL different? Recent studies provide one possible explanation that will require further experimental confirmation.[13] It appears that the APL LIC is very dependent on the PML-RARα for its survival. Studies performed in vitro and in animal models show that ATO potently eliminates PML-RARα from LIC, and that ATRA is synergistic both for PML-RARα proteasomal degradation in LIC and cure of animals in xenograft models. This could represent the first example of targeted therapy for cancer that directly targets the cancer stem cell, and demonstrates just how effective this strategy can be. ■

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ABSTRACT & COMMENTARY

Nilotinib vs. Imatinib for Newly Diagnosed CML

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

Synopsis: *Imatinib at 400 mg daily leads to high response rates for chronic-phase CML, but a subset has suboptimal response and/or toxicity. In this study, 846 subjects were randomized to receive nilotinib, a more selective bcr/abl tyrosine kinase inhibitor, at 300 mg BID or 400 mg BID vs. imatinib at 400 mg daily. The rate of one-year major molecular remission for nilotinib arms was 43%-44%, compared to 22% for imatinib ($p < 0.001$). Similarly, rates of one-year complete cytogenetic remission were superior for nilotinib arms 78%-80%, compared to 65% for imatinib-treated patients ($p < 0.001$). One-year response rates are significantly greater for nilotinib compared to imatinib for newly diagnosed CML.*

Source: G. Saglio, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362:2251-2259.

The 9;22 translocation (a.k.a. Philadelphia chromosome) is the characteristic abnormality underlying chronic myeloid leukemia (CML) that creates a mutant oncogene, BCR/ABL. As a consequence, constitutively activated BCR/ABL tyrosine kinase promotes malignant transformation. Imatinib mesylate (Gleevec) inhibits BCR/ABL tyrosine kinase activity and has changed the paradigm of CML therapy based on frequent and durable remissions in the International Randomized Study of Interferon and STI571(IRIS).[1] Around 20% of patients, however, do not achieve a complete cytogenetic remission, predisposing to disease progression. Further, imatinib infrequently leads to complete molecular response.[2] The more selective ABL kinase binding of second-generation tyrosine kinase inhibitors (i.e., nilotinib and dasatinib) result in significant activity in imatinib-resistant patients, prompting evaluation in the front-line setting.[3,4]

In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) study, nilotinib (at either 300 mg or 400 mg twice daily) was compared to 400 mg daily of imatinib for newly diagnosed chronic-phase CML. Escalation of imatinib to 400 mg twice daily was permitted in patients who had a suboptimal response or treatment failure, as defined by the European LeukemiaNet.[5] The primary endpoint was the rate of major molecular response (MMR) at 12 months, defined as a BCR-ABL transcript level of 0.1% or less in peripheral blood on RQ-PCR assay, as expressed on the International Scale. A total of 846 patients were randomized to either nilotinib 300 mg twice daily (n = 282), nilotinib 400 mg twice daily (n = 281) and imatinib 400 mg daily (n = 283). In the imatinib group, 45 patients were dose-escalated to 800 mg per day. Rates of major molecular response were 44% for nilotinib 300 mg BID, 43% for nilotinib 400 mg BID, and 22% for imatinib ($p < 0.001$ comparing either nilotinib arm to imatinib). For patients at higher baseline risk, based upon Sokal score, the rates of molecular response at 12 months were 41%, 32%, and 17% for nilotinib 300 mg BID, nilotinib 400 mg BID, or imatinib 400 mg QD, respectively. One-year complete cytogenetic response (CCyR) was achieved in 80% of nilotinib 300 mg BID, 78% of nilotinib 400 mg BID, and 65% of imatinib daily ($p < 0.001$). High Sokal risk scores were associated with complete cytogenetic rates of 63%-74% for nilotinib and 49% for imatinib at one year.

Progression to accelerated or blast crises occurred in 14 patients, of whom 11 received imatinib. Thus, the rates of disease evolution were 4% for imatinib and < 1% for nilotinib. Time to progression was reduced with nilotinib ($p = 0.01$). No patients reaching a MMR evolved, whereas three imatinib-treated patients reaching CCyR evolved. Finally, of the 45 patients who received an escalation in imatinib dose, only one had a molecular response and one a complete cytogenetic response.

For adverse events, rates of nausea, diarrhea, vomiting, muscle spasm, and edema, of any grade, were higher for patients in the imatinib group than for those in either nilotinib group. In contrast, rash, headache, pruritus, and alopecia were higher in both nilotinib groups than in the imatinib group. Many patients underwent dose reduction or holding, including 59% receiving 300 mg of nilotinib, 66% receiv-

ing 400 mg of nilotinib, and 52% receiving imatinib. Discontinuations related to toxicity occurred in 5% of patients receiving 300 mg of nilotinib, 9% of those receiving 400 mg of nilotinib, and 7% of those receiving imatinib.

■ COMMENTARY

Although treatment options for CML have dramatically improved, treatment and monitoring have become increasingly complex. Imatinib has been the standard of care for newly diagnosed chronic-phase CML since the drug received approval. Although response rates are quite high, and many durable, a subset of patients do not meet the initial milestone of complete cytogenetic response, and only a minority achieve major molecular remissions.[2,6,7]

This study compared nilotinib at 300 mg or 400 mg administered BID (thus, 600 mg or 800 mg total, respectively) against imatinib 400 mg daily for newly diagnosed CML. Nilotinib resulted in significantly greater rates of MMR, and complete cytogenetic response (CCyR) at one year ($p < 0.001$ in both comparisons). Specifically, nilotinib achieved MMR of 43%-44%, compared to 22% for imatinib. CCyR occurred in 78%-80% of nilotinib patients vs. 65% of imatinib-treated patients. Importantly, in this same issue of the *Journal*, a study comparing dasatinib to imatinib for newly diagnosed CML showed rates of MMR of 46% for dasatinib vs. 28% for imatinib, and complete cytogenetic response of 77% for dasatinib and 66% for imatinib. Further, disease evolution occurred in 3.5% of imatinib, the same rate as the 4% found in this nilotinib trial. Thus, both dasatinib and nilotinib showed similar activity and considerably higher one-year response rates compared to imatinib.

One alternative might be higher-dose imatinib, such as 400 mg BID; however, data for higher-dose imatinib has not shown a benefit in one-year response rates over standard dose, although toxicities are significant.[8]

The major limitation relates to the short follow-up and, thus, limited ability to detect survival differences. Further follow-up will be invaluable to determine long-term disease control and survival.

While the results suggest that with longer-term evaluation, nilotinib (and dasatinib) may improve outcomes, we lack mature data. In addition, other drugs, such as bosutinib, are under review. At present, it remains reasonable to employ imatinib as initial therapy. However, these data also provide a rationale for discussing with patients the use of nilotinib or dasatinib as initial therapy for chronic-phase CML, especially since around 4% of patients in both trials on imatinib had disease evolution even over a short follow-up. Alternatively, an individualized approach can be employed, perhaps reserving front-line, second-generation tyrosine kinase therapy for higher-risk patients, such as high Sokal risk, more advanced disease stages, or only after suboptimal response to imatinib, such as lack of complete cytogenetic response. Finally, for some patients, pre-existing comorbidity may indicate toxicity profiles of certain drugs may be preferred.

In summary, nilotinib leads to significantly improved response rates for newly diagnosed CML at one year. Longer-term follow-up data will confirm the role of nilotinib and other more selective tyrosine kinase inhibitors for initial therapy. ■

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ABSTRACT & COMMENTARY

Xelox for Second-line Treatment of CUP

By William B. Ershler, MD

Synopsis: *In a phase-II study for patients with relapsed or refractory carcinoma of unknown primary, the combination of oxaliplatin and capecitabine was found to be both active and reasonably well tolerated.*

Source: Hainsworth JD, et al. Oxaliplatin and capecitabine in the treatment of patients with recurrent or refractory carcinoma of unknown primary site. A Phase 2 trial of the Sarah Cannon Oncology Research Consortium. *Cancer.* 2010;116:2448–2454.

Carcinoma from an unknown primary site is a fairly common clinical syndrome, accounting for approximately 2%-3% of all cancer diagnoses. Autopsy studies have demonstrated that occult primary lesions within the gastrointestinal tract account for a substantial proportion of CUP.[1] Accordingly, early trials of empiric treatment of CUP used regimens developed for gastrointestinal cancers (e.g., 5-FU; doxorubicin, and mitomycin-C [FAM]). Results were modest, at best, but it is notable that, at the time, these combinations were of only marginal success for gastrointestinal malignancies as well. Subsequently, several taxane/platinum regimens have been investigated for first-line CUP treatment, and have typically produced response rates between 30% and 40%.[2,3] However, for patients with relapse after initial treatment, or for those who did not respond to initial treatment, second-line combinations have met with little success.

Newer regimens for gastrointestinal malignancies, such as 5-FU, leucovorin and oxaliplatin (FOLFOX), 5-FU, leucovorin and irinotecan (FOLFIRI), and capecitabine and oxaliplatin (XELOX) have improved outcomes as treatment in the adjuvant setting or for patients with metastatic disease.[4] However, there is little available information about the use of these combinations as empiric treatment for CUP.

In the current study, Hainsworth and colleagues conducted a community-based phase II trial of combination oxaliplatin and capecitabine (XELOX) in patients with recurrent and/or refractory CUP. For this, patients with histologically confirmed CUP, who had progressive disease despite at least one previous chemotherapy regimen, were treated with oxaliplatin (130 mg/m^2 intravenously on day 1) and capecitabine (1000 mg/m^2 orally twice daily on days 1-14). Treatment cycles were repeated every 21 days. Patients with objective response or stable disease after two cycles continued treatment for six cycles, or until disease progression.

All patients received full doses of both oxaliplatin and capecitabine during the first cycle, and 44 of the 48 patients (92%) received at least two cycles and, thus, were evaluable. Patients received a median of 12 weeks (four cycles) of treatment (range 3-66 weeks), and 15 patients completed six or more cycles.

Nine of 48 patients (19%) had objective responses to treatment; an additional 22 patients had stable disease at the time of first re-evaluation. Of the nine who had responded, five had exhibited no response to initial chemotherapy. After a median follow-up of 17 months, the median progression-free and overall survivals were 3.7 months and 9.7 months, respectively. This regimen was reasonably well tolerated by most patients. Severe myelosuppression was uncommon; only one patient developed febrile neutropenia, and there were no complications related to thrombocytopenia. However, nausea and vomiting were common (54%), and grade 3 neuropathy was observed in two patients. A total of six patients (12%) discontinued therapy because of toxicity.

■ COMMENTARY

The combination of oxaliplatin and capecitabine was found to have activity as a salvage treatment for patients with CUP and, clearly, additional studies are warranted, both as treatment for relapsed or refractory disease, but also as first-line treatment for those with clinical and pathologic features suggesting a primary site in the gastrointestinal tract.

As molecular profiling of cancer samples becomes more available, interventions for CUP are likely to be more directed and less empiric. In fact, such an approach has already been employed. Varadhachary and colleagues at M.D. Anderson, working in collaboration with investigators at the Sarah Cannon Research Institute, have performed a battery of molecular and immunohistochemical analyses on paraffin-embedded tissue from patients with CUP and, for some (particularly those who provided tissue from liver or peritoneal metastases), a colon-cancer profile was apparent (CK20 positive/DK7 negative, CDX2 positive).[5] Furthermore, preliminary data indicate that patients with

CUP who fit this profile respond well to empiric therapy with FOLFOX plus bevacizumab.[6] It is the hopeful expectation that similar examination of metastatic lesions from other primary sites will allow a more educated estimation of the site of primary tumor and, thus, a more focused approach to treatment. ■

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ABSTRACT & COMMENTARY

Eosinophilia/Basophilia in MDS

By William B. Ershler, MD

Synopsis: *In a series of patients with MDS, the presence of peripheral blood eosinophilia, basophilia, eosinopenia, and basopenia were each shown to offer prognostic information with regard to overall survival. This information was shown to be of particular additional value for patients with IPSS-Int-2 risk subgroup.*

Source: Wimazal F, et al. Eosinophilia and basophilia in a larger color of patients with myelodysplastic syndromes. *Cancer*. 2010;116:2372-2381.

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid disorders characterized by abnormal differentiation and maturation of myeloid cells, reduced bone marrow function, and a genetic instability, with enhanced risk to transform to acute myeloid leukemia.[1] Lineage involvement and maturation arrest are considered to have prognostic significance in patients with MDS. However, although the prognostic value of neutropenia, thrombocytopenia, and monocytosis has been documented, little is known about the impact of eosinophils and basophils. Eosinophilia and basophilia are typical features of myeloproliferative disease, most notably chronic myelogenous leukemia, in which basophilia, with or without eosinophilia, is a marker of disease acceleration and adverse outcomes.[2,3] Although less commonly observed, basophilia and/or eosinophilia has also been described in MDS.[4,5]

In the current report, Wimazal and colleagues examined the prognostic significance of eosinophils and basophils among 1,008 patients with de novo MDS. Patients were enrolled from three centers of the Austrian-German MDS Working Group, and were analyzed retrospectively. Blood eosinophils and basophils were quantified by light microscopy, and their impact on survival and leukemia-free survival was calculated using Cox regression.

They found that eosinophilia (eosinophils > 350/lL) and basophilia (basophils > 250/lL) predicted a significantly reduced survival ($p < .05$) without having a significant impact on leukemia-free survival. In multivariate analysis, eosinophilia and basophilia were identified as lactate dehydrogenase (LDH)-independent prognostic variables, with International Prognostic Scoring System (IPSS)-specific impact. Although elevated LDH was identified as a major prognostic determinant in IPSS low-risk, intermediate-1 risk, and high-risk subgroups, the condition "eosinophilia and/or basophilia" was identified as a superior prognostic indicator in the IPSS intermediate-2 risk subgroup.

■ COMMENTARY

Thus, in a relatively larger series of de novo MDS patients, the authors were able to confirm the prognostic importance of both eosinophilia and basophilia, and demonstrated its particular value for patients with INT-

2 risk (per IPSS). Although useful in predicting overall survival, eosinophilia/basophilia, in this series, did not predict progression to AML. This is in contrast to data presented by Matsushima and colleagues.[4]

Curiously, there have also been reports that low basophil counts in patients with MDS predict adverse outcomes, including progression to AML.[5,6] In analysis of the current series, it was discovered that the absolute absence of either peripheral blood basophils or eosinophils was also an independent negative prognostic factor in terms of overall survival.

An explanation for the observed reduced survival among patients with eosinophilia and/or basophilia or eosinopenia or basopenia remains unknown. Although cytogenetic abnormalities were more common in this series in patients with basophilia and/or eosinophilia, no consistent abnormality was reported, and it remains possible that these findings reflect dysregulated marrow function, for which a unifying pathway is not currently apparent.

For clinicians, the findings indicate that abnormal eosinophil or basophil counts (either high or low) are of prognostic value and may ultimately prove useful in determining treatment approach. ■

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CME Questions

1. What advantages does nilotinib therapy provide over imatinib for initial treatment of CML?

a. Confirmed benefit long-term survival
b. Reduced costs
c. Higher cytogenetic response rates at one year
d. Less drug discontinuation for toxicity

2. For patients with metastatic carcinoma from an unknown primary site, the use of oxaliplatin and capecitabine was shown by Hainsworth and colleagues to be:

a. effective (30%-40% response rate) and reasonably well tolerated as front-line therapy.
b. reasonably effective (19% response rate, progression-free survival of 3.7 months) and reasonably well tolerated as second-line therapy.
c. ineffective but reasonably well tolerated as front-line therapy.
d. Ineffective and poorly tolerated as front-line therapy.

3. For patients with MDS, which of the following peripheral blood findings was shown to offer negative prognostic information?

a. basophilia (basophils > 250/uL)
b. eosionphilia (eosinophils > 350/uL)
c. eosinopenia (eosinophils = 0/uL)
d. basopenia (basophils = 0/uL)
e. All of the above

Answers: 1. (c); 2. (b); 3. (e)

CME Objectives

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

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

[IN FUTURE ISSUES]

Breast Cancer During Pregnancy

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, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Coronary Calcium Scores enhance risk prediction

Source: Polonsky TS, et al. *JAMA* 2010; 303:1610-1616.

PROBABLY THE MOST WIDELY RECOGNIZED scoring system for predicting CV risk is the Framingham Risk Score (FRS). The United States Preventive Services Task Force (USPSTF) has recently published the opinion that novel risk markers such as C-reactive protein do not sufficiently enhance risk prediction enough to justify their routine utilization in addition to traditional scoring systems like FRS Coronary Calcium Score (CCS) has a number of appealing attributes that suggest consideration as a powerful prediction tool.

In the Multi-Ethnic Study of Atherosclerosis (MESA) trial of persons without known CHD at baseline, a CCS > 300 was associated with a 10-fold increased risk for CHD events. A critical issue, however, is whether new or additional prediction score tools add meaningfully to existing methods. A metric known as Net Reclassification Improvement (NRI) has been recently proposed to distinguish whether the incremental impact of a scoring system or risk factor upon already existing methods is meaningful.

Using the cohort of MESA (n = 6814 adults; age > 45), Polonsky et al compared risk prediction as derived from FRS vs FRS + CCS. The addition of CCS to FRS resulted in a statistically significant NRI. An additional 23% of persons who experienced CHD events but had not been identified by FRS as high risk were correctly reclassified by the addition of CCS. Similarly, an additional 13% of subjects not classified by FRS as low risk (and who did not suffer events), were reclassified as low risk by the addition of CCS. Whether the preferential (or additional) use of CCS for risk prediction can improve outcomes over traditional risk scores alone will require further definition, although many are already sufficiently encouraged by the predictive power of CCS to currently employ it. ■

Exacerbations of COPD: Not so innocent

Source: Donaldson GC, et al. *Chest* 2010;137:1091-1097.

ACUTE EXACERBATIONS OF COPD (AE-COPD) are sometimes misconstrued as minimally consequential "bumps in the road" along the journey of progressive COPD. Unfortunately, the toxicity of ae-COPD has been underappreciated; ae-COPD are associated with hospitalizations, loss of lung function that is typically not regained, and mortality. Donaldson et al direct our attention to a newly recognized additional burden of morbidity associated with ae-COPD: MI and stroke.

The Health Improvement Network (THIN) database contains anonymized medical records of patients seen by GPs in England and Wales. Over a 2-year period, 25,857 COPD patients provided a dataset with which to compare the incidence of MI and stroke during "stable" periods of COPD with the immediate post-ae-COPD period.

The incidence of acute MI was increased more than 2-fold in the 5-day period immediately following an ae-COPD; similarly, stroke incidence was increased more than 2-fold in the 49-day period immediately post-ae-COPD. Both findings were statistically significant.

No pharmacologic treatment of COPD has been proven to be disease-modifying. Yet, since various pharmacotherapies have been shown to reduce ae-COPD, perhaps such treatments will ultimately be shown to impact disease outcome by affecting the above-mentioned consequences of ae-COPD: increased stroke and MI. ■

Vitamin E, but not pioglitazone, improves NASH

Source: Sanyal AJ, et al. *N Engl J Med* 2010;352:1675-1685.

STEATOSIS IS THE ACCUMULATION OF FAT, derived primarily from triglycerides in hepatic cells. Progressive steatosis can lead to hepatic inflammation, which, when not associated with alcohol, is known as non-alcoholic steatohepatitis (NASH). Obesity and diabetes are the two conditions most commonly associated with NASH. Because as many as 15% of NASH cases may ultimately progress to cirrhosis, effective treatments are eagerly sought.

Since the pathologic underpinnings of NASH often include insulin resistance, hypetriglyceridemia, and type 2 diabetes, pharmacology with thiazolidinediones (TZD) appears logical. Unfortunately, results from pilot trials of TZDs have been conflicting.

The NASH Clinical Research Network, established by the NIDDK, conducted a

placebo-controlled trial of pioglitazone or vitamin E in non-diabetic NASH patients (n = 247). Subjects received 800 IU/d vitamin E, 30 mg/d pioglitazone, or placebo for approximately 2 years. The primary outcome was histologic status of NASH.

At 96 weeks, vitamin E did demonstrate a statistically significant rate of NASH histologic improvement, but pioglitazone did not. Even though there were some favorable histologic effects, neither intervention showed a reduction in hepatic fibrosis, so we remain uncertain about whether vitamin E can impact the development of serious long-term liver disease. Pioglitazone did not achieve an effect on the primary outcome, but explanations for why TZDs may still be considered for NASH therapy are presented by the authors. ■

Best use of home BP monitoring

Source: Pickering TG, et al. *J Am Soc HTN* 2010;4:56-61.

The largest body of information guiding treatment of hypertension (HTN) is based upon office BP management. Nonetheless, home BP monitoring (HBPM) is documented to be a better predictor of CV risk than office BP. For instance, patients with high office BP but low HBPM are recognized to be at substantially lower risk than office BP predicts; similarly, high HBPM pressures compared to office BP portends greater risk than indicated by office BP alone. Simply the fact that HBPM offers the opportunity for many more BP readings than is readily accessible in clinical care provides both a more comprehensive and consistent BP profile.

Recording HBPM twice daily (morning and evening), when averaged over 1 week, provides a sufficient BP profile to help guide management. By HBPM, HTN is > 135/85 mmHg and normotension is < 125/75 mmHg. Borderline HBPM (125-135/75-85 mmHg) merits consideration of 24-hour ambulatory BP monitoring for further clarification. The authors, writing on behalf of the American Society of Hypertension, provide a list of validated home BP monitoring devices at: www.dableeducational.org/. ■

Suicide risk with anticonvulsants

Source: Patorno E, et al. *JAMA* 2010;303:1401-1409.

Although the term "anticonvulsant" is indicative of a therapeutic class, pharmacologically the class is diverse. Despite dissimilarities, an analysis by the FDA (2008) discerned a relative doubling of suicide behavior/ideation in anticonvulsant recipients compared to placebo, resulting in a change in labeling.

The HealthCore Integrated Research Database provides data with which to assess the relative risk for suicidal acts in persons receiving a variety of anticonvulsant agents. During a 5-year interval (2001-2006), almost 300,000 new prescriptions for various anticonvulsants were documented in this population. When compared to treatment with either topiramate or carbamazepine (reference drugs), important distinctions emerged in reference to suicidal acts and violence. For instance, the hazard ratio for suicidal acts was 1.42 for gabapentin, 1.84 for lamotrigine, and 1.65 for valproate, compared to topiramate.

The mechanism by which some anticonvulsants incur an increased suicide risk is not known, despite the recognition that anticonvulsants can have impact upon mood. The first 2 weeks after initiation is recognized to be a higher risk period. Clinicians should be vigilant for behavior or mood changes in patients treated with anticonvulsants, noting lesser apparent risk for topiramate or carbamazepine. ■

For type 2 diabetes, after metformin, what next?

Source: Phung OJ, et al. *JAMA* 2010;303:1410-1418.

In the absence of contraindications, metformin is the preferred initial treatment for most patients with type 2 diabetes (DM2). Unfortunately, monotherapy is unlikely to maintain adequate glycemic control, requiring additional treatment. Although the addition of insulin to metformin is an appropriate next step, and has been labeled Tier 1 in the most recent guidelines published by the American Diabetes Association, some patients are reluctant to use insulin, and the considerable weight gain experienced by some insulin users, as well as risk of hypoglycemia, is problematic.

Among the non-insulin therapeutic choices, there is a great degree of variation in tolerability issues, such as amount of weight gain and frequency/severity of hypoglycemia that may help guide treatment decisions. Phung et al analyzed data from 27 randomized controlled trials (n = 11,198), most of which were 6 months or less in duration, to compare weight changes and hypoglycemia when non-insulin agents were added to metformin.

As might be anticipated, when TZDs, sulfonylureas, and glinides were added to metformin there was a 1.8-2.1 kg weight gain. GLP-1 mimetics, alpha-glucosidase inhibitors, and DPP-4 inhibitors were either weight neutral or associated with minimal weight loss. Sulfonylureas were associated with higher rates of hypoglycemia.

Of course, progressive treatment of DM2 must be individualized, and should include consideration of characteristic tolerability issues such as weight gain and hypoglycemia. ■

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PPIs, *Clostridium difficile*, and Bone Fractures

In this issue: *New reports about proton pump inhibitors and the effects of gastric suppression, pioglitazone vs vitamin E for non-alcoholic steatohepatitis, metformin and vitamin B12 deficiency, and FDA Actions.*

PPIs, C. difficile, and bone fractures

Since H2 antagonists were introduced 30 years ago followed by proton pump inhibitors (PPIs) 20 years ago, there has been speculation whether long-term gastric acid suppression might have adverse effects. Billions of doses later, there is new evidence that chronic PPI use may lead to infections, especially *Clostridium difficile* infection (CDI), and may also contribute to bone fractures.

In the first of several studies published in the May 10 issue of *Archives of Internal Medicine*, researchers looked at more than 101,796 discharges from a tertiary care medical center during a five-year period, reviewing the level of acid suppression therapy and its relationship to CDI. As the level of acid suppression increased, the risk of CDI increased from 0.3% in patients not receiving acid suppressive therapy to 0.6% in those receiving H2 antagonists to 0.9% in those receiving daily PPIs and finally 1.4% in those receiving high-dose PPI therapy. After adjustment for a number of factors including comorbid conditions, age, and antibiotic use, the odds ratio for CDI infections were: 1 with no acid suppressing treatment, 1.53 (95% confidence interval [CI], 1.12-2.10) with H2 antagonist, 1.74 (95% CI, 1.39-2.13) with PPIs, and 2.36 (95% CI, 1.12-2.10) with high-dose PPI therapy. The authors conclude that increasing levels of pharmacologic acid suppression are associated with increased risk of nosocomial *C. difficile* infections, and the risk increases with more aggressive acid suppression (*Arch Intern Med* 2010;170: 784-790).

In a second study from the same journal, researchers from the VA system in Massachusetts performed a retrospective, cohort study of 1166 inpatients and outpatients with CDI to determine if PPI use affected recurrence rates. During treatment for CDI, 45% of patients received a PPI while 55% did not. Recurrent CDI was more common in those exposed to PPIs than in those not exposed (25.2% vs 18.2%). The hazard ratio for recurrent CDI in those exposed to PPIs was 1.42 (95% CI, 1.11-1.82). The risk was higher in patients older than 80 years and in patients exposed to antibiotics not targeted to CDI infections The authors conclude that PPI use during treatment for CDI was associated with a 42% increased risk of recurrence (*Arch Intern Med* 2010;170:772-778).

It has also been postulated that suppressing gastric acid may affect digestion and absorption of certain nutrients, specifically calcium. Although this has never been definitively proven, multiple studies have shown that chronic PPI use is associated with bone fractures. The most recent study, also published in the May 10 issue of *Archives of Internal Medicine*, was a prospective analysis of more than 160,000 women enrolled in the

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Women's Health Initiative study. In more than 1 million person-years of follow-up, there were 1500 hip fractures, 4881 forearm or wrist fractures, 2315 clinical spine fractures, and more than 21,000 total fractures. The multivariate-adjusted hazard ratios for current PPI use was 1 for hip fracture, 1.47 (95% CI, 1.18-1.82) for clinical spine fracture, 1.26 (95% CI, 1.05-1.51) for forearm or wrist fractures, and 1.25 (95% CI, 1.15-1.36) for total fractures. Bone mineral density did not vary between PPI users and non-users. The authors conclude that use of PPIs in women was not associated with hip fractures but was modestly associated with clinical spine, forearm or wrist, and total fractures (*Arch Intern Med* 2010;170:765-771). This study confirms the findings of several large epidemiological studies that suggest that PPI use is associated with increased osteoporotic fracture risk. On May 25, the FDA issued a warning regarding the possible fracture risk associated with high-dose long-term use of PPIs. The Agency will require labeling changes to describe the possible risk.

As noted in these studies, PPI use is associated with risk of osteoporotic fractures and *Clostridium difficile* infections. Other studies have linked the PPIs to a higher risk of hospital- and community-acquired pneumonia, as well as enteric infection such as *Salmonella* and *Campylobacter* gastroenteritis. In an editorial in the May 10 issue of *Archives of Internal Medicine*, Mitchell Katz, MD, notes that of the more than 110 million prescriptions for proton pump inhibitors filled each year, many are for inappropriate indications, making PPIs one of the most overprescribed medication classes in the world. He suggests that "for most patients the adverse effects of PPIs outweigh the benefits" and urges physicians to offer other treatments for dyspepsia, prescribe shorter courses, and consider a trial of discontinuing PPIs in patients who are asymptomatic (*Arch Intern Med* 2010;170:747-748). ■

Pioglitazone vs vitamin E for NASH

Non-alcoholic steatohepatitis (NASH) is a common liver disease that is difficult to treat and often progresses to cirrhosis. A new study compares the thiazolidinedione pioglitazone (30 mg daily) to vitamin E (800 IU daily) in a placebo-controlled trial for 96 weeks in 247 nondiabetic NASH patients. The primary outcomes were standardized scores for steatosis, lobar inflammation, hepatocellular ballooning, and fibrosis as determined by liver biopsy. Vitamin E therapy was associated with a significant improvement in non-alcoholic steatohepatitis (43% vs 19%; $P = 0.001$), but pioglitazone did not show statistical improvement (34% vs 19%; $P = 0.04$). Serum transaminases improved with both treatments, and both reduced hepatic steatosis and lobular inflammation, but neither improved fibrosis. Pioglitazone caused significant weight gain compared to vitamin E or placebo. The authors conclude that vitamin E was superior to placebo for the treatment of NASH in adults without diabetes (*N Engl J Med* 2010;362:1675-1685). ■

Metformin and vitamin B12 deficiency

Monitor your patients on metformin for vitamin B12 deficiency. This is the message of a recent study from the Netherlands. The study enrolled 390 patients with type 2 diabetes on insulin and initiated metformin 850 mg three times a day or placebo for an average of 4.3 years. Metformin treatment was associated with a mean decrease in vitamin B12 concentrations of 19% ($P < 0.001$) and an increase in homocysteine concentrations of 5% ($P = 0.091$). Longer-term treatment with metformin was associated with larger declines in vitamin B12 levels. The authors conclude that metformin likely causes malabsorption of vitamin B12 and recommends routine monitoring of vitamin B12 levels in patients who are treated with metformin (*BMJ* 2010;340:c2181). ■

FDA actions

The FDA has approved a new formulation of oxycodone (OxyContin®) that is designed to discourage chewing, crushing, or dissolving the drug. The FDA admits, however, that although the new formulation reduces the risk of snorting or injecting the drug, it can still be abused by simply ingesting larger doses than recommended. Vocal critics have called for oxycodone's withdrawal from the market due to an explosion in abuse of the drug nationwide and calls this new formulation "too little too late."

The FDA has recommended resuming use of Rotarix® rotavirus vaccine and to continue using RotaTeq® rotavirus vaccine. Rotarix was found to have elements of the porcine circovirus 1 (PCV1) in March, which resulted in an advisory to clinicians to stop using the vaccine. Subsequently, DNA from PCV1 and PCV2 was discovered in the RotaTeq vaccine. The FDA now says that there is no evidence that PCV causes illness or infection in humans while the benefits of the vaccine are substantial. ■

Dear *Clinical Oncology Alert* Subscriber:

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Upon completing this program, the participants:

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

Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers with the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

At the end of the semester, you will receive an evaluation form to complete and return in an envelope we will provide. Please make sure you sign the attestation verifying that you have completed the activity as designed. Once we have received your completed evaluation form, we will mail you a letter of credit. This activity is valid 36 months from the date of publication. This CME activity is intended for the cardiologist.

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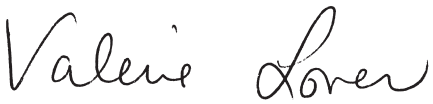

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