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INSIDE

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Lenalidomide Treatment in Patients with Renal Insufficiency: More Neutropenia Observed

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Neutropenia occurs commonly in lenalidomide treated multiple myeloma patients. In this review of a series of newly diagnosed patients, pre-treatment renal dysfunction was clearly associated with increased dose modification-requiring neutropenia.*

Source: Niesvizky R, et al. *Br. J. Haematol.* 2007;138:640-643.

THE INTRODUCTION OF LENALIDOMIDE REPRESENTS A CONSIDered advance in the management of multiple myeloma. An analog of thalidomide, lenalidomide (Revlimid®) has been promoted because it is both more potent and better tolerated than the parent compound.[1] Its effectiveness was established for the treatment of relapsed or refractory myeloma and it is currently under investigation as a first line approach. Typically, lenalidomide is administered 25 mg, orally, daily, on days 1 through 21 of a 28-day cycle. Dose reductions are called for when grade 3 or 4 neutropenia, thrombocytopenia, or other drug-related toxicity occurs. Lenalidomide is primarily excreted through the kidneys and renal insufficiency may affect the incidence of adverse events. The current analysis was undertaken to determine the relationship between preexisting renal insufficiency and the development of grade 3 or higher myelosuppression during lenalidomide therapy.

For this, Niesvizky and colleagues at Cornell University examined data on 72 patients receiving combination lenalidomide and dexamethasone as part of a phase II protocol for the treatment of newly diagnosed multiple myeloma. Eligible patients had symptomatic, measurable disease and a performance status of > 70% (Karnofsky). All patients received lenalidomide and dexamethasone in the 28-day cycle. Dexamethasone 40 mg was given orally once a week. Lenalidomide 25 mg was given orally on days 1 through 21. Concurrent medications included aspirin 82 mg daily,

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omeprazole 20 mg daily, and trimethoprim/sulfamethoxazole three days per week. Of the 72 patients enrolled, 14 had a baseline creatinine clearance of < 0.67 mL/sec (< 40 mL/min).

For grade 3 neutropenia, there were 3 successive dose reductions: level 1; lenalidomide maintained at 25 mg per day but patients treated with granulocyte colony-stimulating factor (G-CSF); level 2; lenalidomide dose reduced to 15 mg per day; level 3, lenalidomide reduced to 10 mg per day; and, level 4; lenalidomide given at 5 mg per day.

Of the 72 patients in the study, 14 developed myelosuppression requiring dose reduction to at least level 1. Of these 14 patients, eight required further reduction to level 2, four patients were reduced to level 3, and one patient to level 4. With regard to renal function, 8 of the 14 requiring dose adjustments had a baseline creatinine clearances of less than 40 mL/min.

Thus, the baseline creatinine clearance of less than 40 mL/min was associated with grade 3 or higher myelosuppression and a need to reduce lenalidomide dosing. The median dose reduction-free survival time for patients with a creatinine clearance of less than 40 mL/min was 6.2 months (95% confidence interval [CI] 1.8 to 8.5 months).

When stratified by baseline creatinine clearance using the 58 patients with a creatinine clearance of greater than 40 mL/min as the reference group, the Kaplan-Meier log-rank test yielded a P value of less than 0.0001. The associated hazard rate was 8.4 (95% CI 2.9 to 24.7, *P*=0.0001) for patients with a creatinine clearance of less than 40 mL/min vs greater than 40 mL/min, indicating an 8.4-fold increased likelihood of lenalidomide dose reduction for these patients.

COMMENTARY

In this analysis of 72 patients treated at a single institution, baseline renal function as estimated by creatinine clearance, predicted both the development of myelosuppression and the need for lenalidomide dose reduction. Other groups reported at last year's American Society of Hematology annual meeting that pretreatment renal insufficiency was associated with lenalidomide-induced thrombocytopenia and platelet transfusion requirements.[2,3]

These findings indicate that special caution must be exercised for those myeloma patients with compromised renal function with regard to lenalidomide treatment. Renal function should be estimated prior to treatment and consideration given to initial lenalidomide dose reductions in an effort to reduce the incidence of severe neutropenia. Additional studies are called for examining the pharmacokinetics, safety and efficacy of lenalidomide in multiple myeloma patients who are to be treated with this regimen. ■

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New Regimen for Poor Risk AML

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *A novel regimen is introduced for the treatment of high-risk acute myelogenous leukemia. In a single-institution phase II trial, flavopiridol, a synthetic flavone, in combination with cytosine arabinoside and mitoxantrone induced durable complete remissions in new patients with secondary leukemia and in those with relapsed disease.*

Source: Karp JE, et al. *Clin Cancer Res.* 2007;13:4467-4472.

Based upon promising phase I data[1], Karp and colleagues at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University performed a phase II trial of timed sequential therapy (TST) using three drugs, flavopiri-

dol (L-86-8275), cytosine arabinoside, and mitoxantrone. Flavopiridol is synthetic flavone derivative,[2] isolated from the stem bark of the Indian tree *Dysoxylum binectariferum* that has been shown to induce apoptosis in a number of neoplastic cell lines, including acute myelogenous leukemia.[3] Based upon its demonstrated mechanism of action there was rationale to combine flavopiridol with other cell-cycle specific drugs. The Hopkins group chose cytosine arabinoside and mitoxantrone based upon both theoretic considerations and activity demonstrated in the Phase I trial.

For the current study, flavopiridol was administered at a dose of 50 mg/m2 over 1 hour daily X 3 beginning on day 1. Cytosine arabinoside (ara C), 2 gm/m2 as a 72 hour continuous infusion began on day 6. Mitoxantrone, 40 mg/m2 was administered as a single bolus infusion (30-60 minutes) on day 9, 12 hours after completion of the ara C infusion. Patients who achieved complete or partial remission after cycle 1 were eligible to receive a second cycle beginning no earlier than 30 days after cycle 1. To ameliorate the secretory diarrhea associated with flavopiridol[4] octreotide was administered q8 hours prior to and for one day after flavopiridol infusions. Other supportive measures, including antibiotic and antiviral prophylaxis were also aggressively maintained.

A total of 62 patients were entered on this phase II trial. Patients had either poor-risk, newly diagnosed (n=15), relapsed (n=24) or refractory AML (n=23). The 15 patients with newly diagnosed AML had a median age of 61 years, with 10 having antecedent myelodysplasia, 2 treatment-related AML and 3 with prior myeloproliferative disease. All newly diagnosed patients had at least 2 poor-risk factors (age >60, secondary AML, adverse cytogenetic features, or poor performance status (ECOG PS ≥ 2). For the 24 patients with relapsed AML, the median duration of CR was 9 months (range 4-22 months). Flavopiridol caused a >50% decrease in peripheral blood blasts in 44% by median day 2 and >80% decrease in 26% by day 3. Self-limited tumor lysis occurred in 53%. Three died during therapy (2 multi-organ failure, 1 fungal pneumonia). Complete remissions were achieved in 12 of 15 newly diagnosed secondary AML, in 18 of 24 who were in first relapse after a short CR from primary therapy, and in 2 of 13 who had primary refractory disease and 0 of 10 who were refractory after multiple chemotherapy regimens. Disease free survival for all CR patients was 40% at two years, and for those with newly diagnosed secondary AML it was 50% at two years.

Tumor lysis syndrome occurred in 53% but was manageable. Other adverse effects included mucositis and cardiac arrhythmia but these were, for the most part, grade 2 or less.

COMMENTARY

Thus, flavopiridol has anti-AML activity directly and in combination with ara-C and mitoxantrone. Using a timed, sequential protocol, durable CRs were achieved in a significant portion of patients with newly-diagnosed secondary AML and in those with relapse after a short initial remission. The data compare favorably with other sequential regimens used in the same setting[5,6] and provide optimism that more effective therapy for these difficult to treat leukemias is around the corner. ■

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Low Risk of CHF from Imatinib

ABSTRACT & COMMENTARY

By Andrew Artz, MD, MS

Division of Hematology/Oncology, University of Chicago, Chicago, IL

Dr. Artz reports no financial relationship to this field of study.

Synopsis: *Imatinib has recently been reported to cause CHF, but the clinical incidence is unclear. The investigators reviewed 1276 imatinib treated patients on clinical trials at a single institution and found 22 cases (1.7% incidence) of CHF symptoms and/or low ejection fraction (EF). Most cases (18/22) occurred in those having pre-existing cardiac risk factors. CHF was more common in older patients. Imatinib dose did not correlate with CHF. In summary, the incidence of CHF in imatinib treated patients was similar to the expected population incidence. Prospective trials are warranted to precisely determine the incidence and attribution of imatinib to CHF.*

Source: Atallah E, et al. Congestive heart failure is a rare event in patients receiving imatinib therapy. *Blood.* 2007; 110:1233-1237.

The Philadelphia chromosome creates the Bcr-Abl fusion protein, which characterizes chronic myeloid leukemia (CML). The tyrosine kinase inhibitor imatinib (Gleevec™, originally known as STI-571) competitively inhibits bcr-abl activity as well as other signal transduction pathways. The high activity and low toxicity lead to rapid incorporation into clinical practice.[1] Concern about serious cardiac toxicity recently emerged when a series of 10 cases of CHF during imatinib treatment were reported.[2] Animal models supported a pathophysiologic link. The Abl protein plays a role in cardiac cell maintenance, which is perturbed when exposed to imatinib. The lack of confirmation and estimates of incidence or risk factors have left a major void for this now commonly used treatment. In this report, Atallah and colleagues from the MD Anderson Cancer Center report on the incidence of cardiac toxicity during imatinib treatment.

Records from patients receiving imatinib from 1998 to 2006 on clinical trials were reviewed. The analysis focused on cardiac symptoms, testing (left ventricular ejection fraction), cardiac risk factors, and serious and/or unexpected adverse events. CHF was defined using the Framingham criteria or the development of asymptomatic low ejection fraction (<50%).

There were 1276 patients receiving imatinib on clinical trials. The median age was 52 years (range 15-84) with a median follow-up of almost 4 years. Twenty-two patients developed CHF during therapy. Five of these cases were previously reported in the initial publication on imatinib cardiac toxicity.[2] The overall incidence was 1.7% (22/1276). The ejection fraction was objectively evaluated in 15 cases, 9 of whom showed an EF below 50%. CHF incidence increased with advancing age: 0% if under 45 years, 0.3% (01/322) between 45-55 years, 1.7% (5/291) for ages 56-65 years, 2.8% (6/211) in the 66-75 cohort, and 9.3% (4/43) when aged 76 to 85 years. Imatinib dose showed no relationship to developing CHF. Prior cardiac risk factors were present in 18/22 patients in whom CHF developed.

COMMENTARY

Much concern has been generated since investigators reported a series of 10 CHF cases in imatinib treated patients. The postulated mechanism of CHF was perturbation of the Abl protein's normal role in cardiac maintenance.[2]

In this retrospective review of over 1000 thousand imatinib treated patients at a single institution, the authors suggest imatinib induced congestive heart failure is uncommon. Only 1.7% of patients developed CHF as assessed by symptoms and/or low EF. Older age and preexisting cardiac conditions were the major risk factors. The median age for cases was 70 years vs 52 years for those without CHF (P= 0.001). Most patients who developed CHF (18/22) had at least one cardiac risk factor.

As an observational study, patients were not prospectively followed. The 1.7% incidence may be an underestimate as ascertainment may be incomplete or subtle cardiac symptoms may be missed. Further, as a cohort of patients enrolled in clinical trials, one can assume better health than the average patient treated in community clinical practice. The relatively young age (median 52 years) supports this notion. Alternatively, imatinib induced cardiac damage may be rare to non-existent. The incidence of CHF was similar to the population incidence of CHF and imatinib symptoms of edema or fatigue could be mistaken for CHF, leading to misclassifying cases as CHF. Other large series of imatinib treated patients mirror the results reported by Atallah.[3,4]

How do we reconcile the seemingly conflicting results? The true incidence requires a prospective analysis of imatinib-treated patients for CHF. Although the exact incidence remains unknown, the data are reassuring that serious CHF occurs infrequently in imatinib treated patients. These findings translate into clinical practice. The potential risk of CHF should not prevent

imatinib treatment when indicated. For those who develop CHF symptoms during imatinib therapy, a cardiac evaluation is necessary irrespective of imatinib treatment. The role of cardiac biopsy is unknown although a specific imatinib associated pattern of damage has been suggested. In most cases, discontinuation of imatinib is not necessarily required, although severe CHF and/or lack of cardiac risk factors would prompt considering alternative medications. We must keep in mind that other treatments have toxicities as well and may not necessarily be safer. For example, dasatinib has been approved for CML; however, this tyrosine kinase inhibitor may lead to pericardial or pleural effusions, concerning side effects when switching because of CHF. Moreover, the new generation of tyrosine kinase inhibitors (eg, dasatinib, nilotinib) have a theoretically risk of CHF as they also inhibit the Abl protein.

In conclusion, imatinib induced CHF is uncommon but prospective trials will be required to define the precise incidence and attribution. ■

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Combination Chemotherapy for Unknown Primary

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Carcinoma of unknown primary remains a management problem without an established approach demonstrated to prolong survival. In a phase II study, the combination of carboplatin, gemcitabine, and capecitabine was shown to be fairly well tolerated and, for certain subsets, effective in producing transient tumor regression.*

Source: Schneider BJ, et al. *Cancer.* 2007;110:770-775.

Optimal treatment for patients who present with metastatic cancer of unknown primary remains unsettled. Such presentation is not unusual, accounting for approximately 2% of all newly diagnosed cancer.[1] Although difficult to establish in individual cases, autopsy series indicate the lung, pancreas and hepatobiliary tree are the most common sites of original disease.[2] To date, no treatment regimen has been clearly demonstrated to provide significant prolongation of survival, particularly for those with moderately or well differentiated adenocarcinomas involving the liver.[3]

Schneider and colleagues report a phase II trial of carboplatin, gemcitabine and capecitabine in 33 patients with unknown primary. Treatment consisted of 21 day cycles. Carboplatin dose was targeted to an area under the curve (AUC) of 5 (mg/ml x min) and administered as a 30 minute intravenous infusion on day 1, just after the gemcitabine dose. The gemcitabine dose is 1000 mg/m2 and given over 30 minutes on days 1 and 8. Capecitabine was taken orally twice daily for 14 days at a total daily dose of 1600 mg/m2. Treatment continued for up to 8 cycles with demonstration of objective response or disease stability.

Over a 4.5 year period (August 2001 through January 2006) 33 patients were enrolled. The median age at study entry was 58 years and no patients had received prior chemotherapy or radiation for this condition. A median of 5 cycles (range 1-8) was administered to each patient. In general the treatment was well tolerated. The most common grade 3-4 toxicities were neutropenia (67%) and thrombocytopenia (48%). All 9 patients with an ECOG performance score of 2 had grade 3/4 hematologic toxicity compared to 10 of 24 patients who were ECOG PS 0-1.

Thirteen of the 33 patients had a partial response to treatment and the median response duration was 3.9 months (1.4-11.2 months). By using intent-to-treat analysis, the median time to treatment failure was 4.5 months (95% confidence interval [CI], 2.8-5.7). Median progression free survival time was 6.2 months (95% CI, 5.4-8.0 months), and at 6 months over half (54.5%; 95% CI, 36.3%-69.6%) were alive and progression free. Median survival was 7.6 months (95% CI, 6.3-14.1 months), and the 1-year and 2-year survival rates were 35.6% (95% CI, 19.7-51.8%) and 14.2% (95% CI, 4.6%-29.1%), respectively.

Serum tumor markers (CEA and CA19-9) were evaluated in a subset. Patients with a > 50% drop in a marker survived longer than those with elevated markers that did not drop (median survival, 19.4 months vs 7.1 month, $P = 0.03$).

COMMENTARY

Over the past two decades there has been a significant reduction in the absolute numbers of those diagnosed "unknown primaries." This, no doubt, is the result of better imaging and bolder pathologists. Yet, despite this, there remains less than acceptable treatment success and

no single regimen stands ahead of the rest. Among many reasons for this is the likely great heterogeneity in reported series. Perhaps with the rapidly advancing molecular technology, there will be more precise identification of tumor type, greater homogeneity in clinical trials and more specific and directed therapies. Yet, even if we become capable of defining lung, pancreas or biliary tree primary, there will not be much satisfaction until treatments for these tumors yields greater success.

That stated, oncologists faced with an individual with metastatic cancer of unknown primary should attempt to make an educated prediction whether the tumor arose from above or below the diaphragm. If lung primary is suspected, a platinum/taxane regimen might offer greater chance for treatment response. However, if the suspected primary is below, the triplet offered in this report seems as effective as any. For patients with good performance status, it is fairly well tolerated and for those with liver involvement, a group known to have particularly poor prognosis, a response rate of 40% is remarkable. ■

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More on Breast Cancer in the Elderly

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a national survey conducted in Italy, data from 1085 women 65 years and older with newly diagnosed breast cancer was analyzed with regard to stage at presentation, histological features and treatments provided. By dividing the overall cohort into age subsets, the data indicate that those in the oldest group are more likely to present with larger tumors and also be treated in the adjuvant setting with endocrine manipulation alone. However, the oldest group were more likely to be hormone receptor positive. Other features of tumor aggressiveness, such as Ki67 and Her-2-neu expression were not significantly different across the various age subsets.*

Source: Mustacchi G, et al. *Ann Oncol.* 2007;18:991-996.

ONCOLOGISTS HAVE BECOME INCREASINGLY aware of geriatric issues relating to cancer management. These issues are particularly relevant to breast cancer because the majority of patients are over the age of 65 years and there are important and well recognized age-associated differences in tumor biology, screening and treatment. To achieve a better understanding of current attitudes and practices, the National Oncological Research Observatory on Adjuvant Therapy (NORA), operational throughout Italy, consecutively enrolled over 3500 breast cancer patients from 2000 through 2002, of which 1085 were 65 years or older. Of these, 40% were aged 65-69 years, 31% were 70-75 years and 29% were older than 75 years.

The analysis undertaken pertained to relevant clinical parameter and were described in the context of the three age subsets: 65-69, 70-75, and >75 years. A summary of their findings are as follows:

Diagnosis: Almost 50% of cases were diagnosed by self-exam and the percentage increased significantly by age group. Approximately 40% of those in the 65-69 year old group discovered their breast cancer by self exam compared to nearly 70% for those over 75 years. Conversely, routine periodic screening uncovered the breast cancer in 31% of those patients in the 65-69 year old group compared with only 11% in the over 75 year old group.

Comorbidities: Not surprisingly, the number of comorbidities increased with age. Significant comorbid disease was reported in 38% of those between 65-69 years compared with 70% for those over 75 years.

Tumor biology: Although histological type did not vary significantly among the three age subsets, tumor size was related to age. The number of T1 tumors decreased from 57.4% to 50.8% to 46.0% for the groups aged 65-69 years, 70-75 years, and >75 years respectively ($\chi 2$ for trend = 12.430; P = 0.0004). Reciprocal increases in larger tumors were seen with each advancing age group.

In contrast, hormone receptor positivity increased with age. Overall, 85.5% had at least one positive receptor (estrogen or progesterone) and 67.9% were positive for both. Estrogen and Progesterone positivity was present in 63.6%, 68.6%, and 73.1% for groups aged 65-69 years, 70-75 years, and >75 years respectively ($\chi 2$ for trend = 7.886; P = 0.005). Her-2-neu/c-erB2 status and proliferation index, evaluated by Ki67/MB1 staining, were not different in the age groups.

Axillary node dissections were performed in 95.5% of this group. Overall, 56.7% had negative nodes, 23.9% had one to three positive nodes, 12.3% had 4-10 positive nodes and 7.1% had >10 positive nodes, and there was no age-related difference. However, the median number

of examined nodes declined with age of the patient ($\chi 2$ for trend = 10.856; $P = 0.001$).

Treatment Decisions. Of the entire series, only 4.1% did not receive some form of systemic adjuvant treatment. Overall, 52.4% received endocrine therapy alone, 13% chemotherapy alone, and 30.4% both endocrine and chemotherapy. The use of endocrine therapy alone increased significantly with age (37.1% to 51.9% to 74.8% for groups aged 65-69 years, 70-75 years, and >75 years respectively and conversely, chemotherapy (alone or followed by endocrine treatment) decreased from 62.2% to 44.7% to 17.2% for groups aged 65-69 years, 70-75 years, and >75 years respectively (2 for heterogeneity = 146.51; $P = 0.001$).

COMMENTARY

This extensive survey performed throughout Italy was designed to be representative of the practice patterns as a whole, as great care was taken to include academic and community practices distributed throughout the country.[1] This report includes data only for the over 65 year olds and demonstrates changes in stage at presentation, hormone receptor positivity, and treatment aggressiveness within the age group subsets. None of the findings will come as much of a surprise to practicing oncologists, although the data is a valuable addition to the literature, providing evidence for trends that we knew from experience to be likely. It was a little surprising to see the high number of axillary node dissections performed (95.5% of the entire group had pathological analysis of axillary nodes, albeit a slightly reduced number of nodes per patient was available for the oldest subset). Similarly impressive was the observation that only 4% of the group received no form of systemic adjuvant therapy. The detailed and careful NORA methodology[1] make it unlikely that there was sample bias such that only the most robust of the elderly were included. This is somewhat in contrast to current perceptions regarding workup and treatment of breast cancer in the elderly, particularly those of very advanced age or with comorbidities.[2-4]

Measures of tumor aggressiveness, such as histological features, markers of proliferation or the over expression of Her-2-neu were not demonstrably different within the various subsets presented here. However, it will be of interest to see the entirety of the NORA data in this regard because differences between young and old might be much more apparent than when comparing old vs very old, as in the current report.

The NORA report is a welcome addition to the literature. There has been a substantial development of interest in geriatric oncology and this represents the largest observational series of elderly breast cancer patients. We look forward to ongoing analysis with regard to treatment success and overall survival in this well characterized cohort. ■

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CME Questions

41. Lenalidomide administered at 25mg/day for 21 of 28 days in patients with myeloma and coexisting renal insufficiency is associated with dose-modification-requiring levels due to:

a. neutropenia
b. thrombocytopenia
c. both neutropenia and thrombocytopenia
d. neither neutropenia and thrombocytopenia.

42. Which of the following is a common but avoidable toxicity of flavopiridol treatment?

a. cardiomyopathy
b. secretory diarrhea
c. hand foot syndrome
d. rash

43. Based upon the report of Atallah and investigators, what is the association between imatinib and congestive heart failure (CHF)?

a. It is frequent; over 10% of imatinib treated patients develop CHF
b. The development of CHF is not related to cardiac risk factors in imatinib treated patients
c. CHF occurs more frequently in older patients treated with imatinib
d. CHF is related to imatinib dose

44. In the phase II trial of carboplatin, gemcitabine and capecitabine for unknown primary, the most prevalent grade 3/4 toxicity was:

a. anemia
b. hand foot syndrome
c. diarrhea
d. neutropenia

45. In the NORA study of breast cancer in elderly women, which of the following features was different in the oldest age subset (>75 years) compared to those in the 65-69 year subset?

a. tumor size
b. axillary node positivity
c. Her-2-neu expression
d. % receiving adjuvant treatment

Answers: 41 (c); 42 (b); 43 (c); 44 (d); 45 (a)

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Stopping Statins in At-Risk Patients — Just Too Risky

In this issue: *Make sure your patients don't stop statins after a stroke or surgery; MRSA is becoming more resistant to mupirocin; new asthma treatment guidelines; and FDA approvals and warnings.*

Stopping statins, even briefly, after stroke or cardiovascular surgery increases vascular complications according to 3 new studies. Spanish investigators looked at 89 patients who were on chronic statin therapy and were admitted with acute stroke. Half were randomized to statin withdrawal for the first 3 days after admission, while the other half immediately received atorvastatin 20 mg/day. After 4 days, the statin withdrawal group was also started on atorvastatin. The primary outcome was death or dependence after 3 months as defined by modified Rankin scale of 2 or more. After 3 months, 60% of those in the statin withdraw group were disabled to the point of dependence compared with 39% of those that continued statin therapy (P = 0.043). Early neurologic deterioration was also far greater in the statin withdrawal group (65.2% versus 20.9%; $P < 0.0001$). Statin withdrawal patients also had greater infarct volume (P = 0.002). The authors conclude that statin withdrawal in the first few days after stroke is associated with a markedly increased risk of death or dependency at 90 days; hence, treatment should continue the acute phase of an ischemic stroke (*Neurology* 2007; 69:904-910).

In another study, researchers in Italy looked at stroke patients who discontinued statins after discharge from the hospital. The study population included 631 stroke patients (322 men, 309 women) without evidence of heart disease. All patients were discharged on a statin, but 38.9% discontinued the drug within 12 months. In the 12 months of follow-up, 116 patients died. After adjustment for all confounders and interactions, the hazard ratio for mortality in patients who quit a statin was 2.78 (95%CI, 1.96-3.72; P = 0.003) or nearly 3 times higher risk of death (*Stroke* 2007, published online ahead of print 8/30/07).

Another study from the Netherlands looked at a brief interruption in statin therapy associated with major vascular surgery. Nearly 300 patients on statins underwent major vascular surgery, and statin therapy was interrupted in the perioperative period in 70 patients for mean duration of 3 days. An association was observed between statin discontinuation and an increase risk of postoperative troponin release (HR 4.6) and the combination of MI and cardiovascular death combined (HR 7.5). Because many surgical patients are NPO and unable to take oral statins, and there's no intravenous statin available, the only extended release statin was tried on a subset of patients preoperatively. Patients receiving extended-release fluvastatin had fewer perioperative cardiac events compared to other statins (*Am J Cardiol* 2007; 100:316-320). The message of these studies is that statin interruption, even for a brief period during hospitalization, may lead to serious adverse events in patients at risk.

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Mupirocin Less Effective Against MRSA

Mupirocin (Bactroban) is becoming less and less effective against MRSA, even in hospitals with low levels of mupirocin use. Researchers from Washington University in St. Louis performed nasal swab cultures for MRSA in all patients admitted to their surgical intensive care unit (SICU) on admission, weekly during hospitalization, and at discharge. Of the 302 positive MRSA isolates, 13.2% were resistant to mupirocin, with 8.6% having high-level resistance. Patients with mupirocin-resistant MRSA were more likely to be older, have a history of a previous admission in last year, and had higher in-hospital mortality. The authors conclude that patients carrying mupirocin-resistant MRSA acquired it through contact with the health-care system; the strains were probably not acquired in the SICU (*Clin Infect Dis* 2007; 45:541-547). Mupirocin is commonly used to decolonize patients who are *staph aureus* carriers or have nasal colonization with MRSA. With resistance patterns increasing nationwide, this strategy may need to change.

New Guideline for Asthma Diagnosis/Management

The National Asthma Education and Prevention Program has issued an update to their clinical practice guidelines for diagnosis and management of asthma (Expert Panel Report 3 [EPR-3]). The new guideline emphasizes the importance of asthma control and highlights 4 areas of emphasis including assessment and monitoring, patient education, control of environmental factors and other asthma triggers, and pharmacotherapy. The new guideline recommends continued use of a stepwise approach to asthma control in which medication doses or types are stepped up or down as needed based on asthma control. Recommendations now are based on 3 age groups, 0-4 years, 5-11 years (a new category), and 12 years and older.. The new age group was added because of evidence that children respond differently to medications than adults. The entire guideline can be found at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf .

FDA Actions

The FDA announced on August 14 that manufacturers of rosiglitazone (Avandia) pioglitazone (Actos), and other combination medications containing the 2 drugs will be required to add a "black box" warning to their labeling to reflect the risk of heart failure associated with the 2 drugs. Both drugs have been associated with reports of significant weight gain and edema, and some cases continuation of therapy has lead to poor outcomes including death. The black box warning advises health-care professionals to carefully observe patients taking these drugs for signs and symptoms of heart failure including rapid weight gain, shortness of breath, edema. The warning also recommends not starting either drug in patients with a history of congestive heart failure. The agency continues to review rosiglitazone for the possible increase risk of myocardial infarction associated with use of the drug.

The FDA has approved a new indication for zoledronic acid (Reclast) as a once-a-year treatment for postmenopausal osteoporosis. Reclast is administered as an annual 15-minute intravenous infusion. The drug is a bisphosphonate similar to oral bisphosphonates such as alendronate and risedronate.

Anesiva has received approval to market lidocaine topical powder intradermal injection system (Zingo) to provide local analgesic prior to venipuncture or peripheral intravenous cannulation in children ages 3-18. Zingo is a single-use helium powered system that is administered 1-3 minutes prior to needle insertion. The system is also being studied in trials of adults.

The FDA has approved a new combination of carbidopa, levodopa, entacapone (50 mg/200 mg/200 mg) for the treatment of Parkinson's disease. The new preparation helps reduce the pill burden for Parkinson's patients on multiple medications. Carbidopa/levodopa/entacapone will be marketed by Orion Corporation as Stalevo.

Omrix Biopharmaceuticals has received approval to market human thrombin (Evithrom) to promote blood clotting and control bleeding during surgery. Evithrom is the first human thrombin approved since 1954 and the only product currently available for this indication. It is applied to the surface of bleeding tissue during surgery and may be used in conjunction with absorbable gelatin sponge. Other thrombins currently on the market are derived from cattle plasma.

Nursing mothers who were taking codeine may put their babies at risk of morphine overdose if they are "ultra-rapid metabolizers of codeine," a condition that may affect up to 28% of the population. Codeine is generally recommended for nursing mothers as a cough suppressant and pain medication; however, ultra-rapid metabolizers quickly convert codeine to morphine and excrete it in breast milk. At least one infant death has been associated with this condition. The FDA has issued warning regarding codeine use by nursing mothers, recommending that mothers observe their infants closely while taking the medication for signs of morphine overdose including sleepiness, difficulty breast feeding, breathing difficulties or limpness. ■