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ABSTRACT & COMMENTARY

Cancer Prevention by Aspirin: A New Evaluation of Existing Data

By William B. Ershler, MD

SYNOPSIS: By a systematic review of observational (case-control and cohort) studies, data regarding aspirin use and cancer risk were compared to data obtained from randomized clinical trials. In general, there was very good correlation regarding reduced risk for several types of cancer and the development of metastatic disease. The analysis provides confidence that observational studies can be of value in addressing the many outstanding questions regarding aspirin and cancer prevention.

SOURCE: Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: A systematic comparison of evidence from observational studies versus randomized trials. *Lancet Oncol* 2012;13:518-527.

It has been proposed that aspirin is effective in the prevention of cancer. Data derived from randomized trials of aspirin in prevention of vascular events showed that daily aspirin reduced the incidence of colorectal cancer and several other cancers[1] and reduced metastasis.[2] However, statistical power was inadequate to establish effects on less common cancers and on cancers in women. Newly designed randomized trials projected to gather data for 20 or more years would be an optimal but impractical methodological approach. However, careful evaluation of existing observational studies might also provide insight. To determine the reliability of data derived from such studies compared to that from randomized controlled trials, Algra and Rothwell performed a systematic evaluation of the effects of aspirin on cancer outcomes from both types of investigation.

For this, the authors searched for case-control and cohort studies published from 1950 to 2011 that reported associations between aspirin use and risk or outcome of cancer. For the observational studies, papers were considered eligible for this analysis if they reported results of case-control or cohort studies of use of aspirin or nonsteroidal anti-inflammatory drugs (NSAID) in the context of cancer development. For the randomized trials, the current analysis required a randomization to aspirin vs no aspirin and a mean scheduled duration of treatment for 4 years or more. Of the large existing literature, 150 case-control studies and 45 cohort

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studies were considered appropriate for the final analysis.

Associations were pooled across studies by meta-analysis and stratified by duration, dose, and frequency of aspirin use and by stage of cancer. They went on to compare associations from observational studies with the effect of aspirin on 20-year risk of cancer death and on metastasis in the recent reports of randomized trials.

In case-control studies, regular use of aspirin was associated with reduced risk of colorectal cancer (pooled odds ratio [OR] 0.62, 95% confidence interval [CI] 0.58–0.67), and there was good agreement with the effect of daily aspirin use on 20-year risk of death due to colorectal cancer from the randomized trials (OR 0.58, 95% CI 0.44–0.78). Similarly consistent reductions were seen in risks of esophageal, gastric, biliary, and breast cancer. Overall, estimates of effect of aspirin on individual cancers in case-control studies were highly correlated with those in randomized trials ($r = 0.71$, $P = 0.0006$), particularly with regard to gastrointestinal cancers. Estimates of effects in cohort studies were similar when analyses were stratified by frequency and duration of aspirin use, were based on updated assessments of use during follow-up, and were appropriately adjusted for baseline characteristics. Although fewer observational studies stratified analyses by the stage of cancer at diagnosis, regular use of aspirin was associated with a reduced proportion of cancers with distant metastasis (OR 0.69, 95% CI 0.57–0.83), but not with any reduction in regional spread (OR 0.98, 95% CI 0.88–1.09), consistent again with the findings in randomized trials.

COMMENTARY

Although cancer prevention is high priority, cancer prevention studies are methodologically difficult and very expensive. With regard to aspirin, we have known for decades that this drug has potential for reducing cancer development and/or spread on the basis of its effects on platelet function,[3] inhibition of COX-2,[4] or by other pro-apoptotic effects.[5-7] Yet, until recently there have been few randomized cancer prevention trials. Recently, aspirin was shown to reduce colorectal cancer in patients with the precancerous Lynch syndrome,[8] but cancer prevention within the general population has not been adequately demonstrated by such methodology. That stated, recent analysis of data from trials in which aspirin was used for stroke or other vascular disease prevention have now clearly been shown to reduce the risk of certain cancers, particularly in men.[1]

The data reported in the current report are welcome because they indicate the value of case-control and careful cohort study analyses as they demonstrate very good correlation with observations from the randomized trials. Accordingly, such methodology will be useful in addressing the large number of outstanding questions, such as dose, schedule, and duration; which tumors are likely to be prevented; and whether aspirin could reduce the development of metastases when applied in an adjuvant setting. ■

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ABSTRACT & COMMENTARY

Aspirin and Statin Nonuse Associated With Early Biochemical Failure After Prostate Radiation Therapy

By Samir P. Kanani, MD

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

SYNOPSIS: In a large retrospective series, 2051 men with clinically localized prostate cancer received definitive radiation therapy (RT) alone. The rates of aspirin use and statin use were 36% and 34%, respectively. The primary endpoint was IBF (interval to biochemical failure) of < 18 months. With a median follow-up of 75 months, univariate analysis demonstrated that an IBF of < 18 months was associated with aspirin nonuse, statin nonuse, anticoagulant nonuse, cardiovascular disease, and PSA, but not Gleason score, age, RT dose, or T stage. On multivariate analysis, only aspirin nonuse and statin nonuse were associated with an IBF of < 18 months.

SOURCE: Zaorsky NG, et al. Aspirin and statin nonuse associated with early biochemical failure after prostate radiation therapy. *Int J Radiation Biol Phys* 2012; [Epub ahead of print].

Between 1989 and 2006, 2051 men with localized prostate cancer received definitive RT (median dose = 76 Gy) without androgen deprivation therapy. 3DCRT was used to treat 64% of the patients and the remainders were treated with intensity-modulated radiotherapy. Approximately 90% of the patients were low- and intermediate-risk patients, according to the National Comprehensive Cancer Network criteria. Thirty-six percent reported aspirin use either at the time of radiotherapy or during follow-up and 34% reported statin use. Cardiovascular disease was present in 35% of patients.

The primary objective of this study was to retrospectively analyze this cohort of men to evaluate whether the use of statins and/or aspirin could prolong the interval to biochemical failure to > 18 months. The authors chose the surrogate endpoint of interval to biochemical failure (IBF) < 18 months as a cutoff, as this has been shown to be the single strongest predictor of distant metastasis, prostate cancer survival, and overall survival after radiation therapy (RT). On univariate analysis, an IBF of < 18 months was associated with aspirin nonuse ($P < 0.0001$), statin nonuse ($P < 0.0001$), anticoagulant nonuse ($P = 0.0006$), cardiovascular disease ($P = 0.0008$), and initial PSA level (continuous variable) ($P = 0.008$). Gleason score (2-6 vs 7 vs 8-10), age, RT dose, and T stage were not significant in predicting an IBF < 18 months.

On multivariate analysis, aspirin nonuse ($P = 0.0012$) and statin nonuse ($P = 0.0002$) were associated with an IBF < 18 months. Aspirin nonuse had an odds ratio (OR) of 2.052 (95% confidence interval [CI], 1.3-3.1) for an IBF < 18 months, and statin nonuse had an OR of 2.47 (95% CI, 1.53-3.97). The authors conclude that in men receiving RT for prostate cancer, aspirin and statin nonuse were associated with the early development of biochemical failure.

COMMENTARY

The above summarized study definitely adds some clinical validity to the vast in vitro data regarding the antineoplastic effects of aspirin and statins. Aspirin is well known for its properties of inhibiting cyclooxygenase 2 (COX-2), which is upregulated in prostate cancer, and overexpression correlates with higher grade tumor.[1] Aspirin has been shown to promote apoptosis through a variety of cellular mechanisms, including the upregulation of the Par-4 gene[2] and inducing the expression of proapoptotic proteins Bax and Bak.[3] Statins have demonstrated antineoplastic effects and have immunomodulatory effects via the effect on fatty acid synthesis.

The series by Zaorsky et al confirms a number of previously reported series that show a benefit in delaying biochemical failure patients with prostate cancer on anticoagulant therapy and/or statins. To date, no series has demonstrated on overall survival advantage.[4-6] Certainly the population at risk for prostate cancer has a number of competing risk factors for mortality and it is easy to understand why no clear survival advantage could be found. It will be important to prospectively study the use of these drugs in the management of prostate cancer in respect to other clinically important endpoints such as metastasis-free survival. Also, it is crucial to point out that these retrospective series confirm an association between statins, aspirin, and biochemical failure, but by no means demonstrate causation between drug use and risk of biochemical failure. Drugs such as aspirin and

statins have their own side effect profile that must be weighed carefully against any potential benefit in delay/prevention of biochemical failure in robust prospective trials. Optimal dosing schedules need to be determined as well. In my opinion, the strong association seen in this trial needs further investigation and the use of statins and aspirin should not be recommended until prospective trials validate that there is a causation between statin and aspirin use and biochemical outcomes. ■

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ABSTRACT & COMMENTARY

Controlling Pegfilgrastim Bone Pain

By Gary R. Shapiro, MD

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

SYNOPSIS: This randomized, placebo-controlled, Phase 3 clinical trial showed that the majority of patients treated with pegfilgrastim experience bone pain, and that taking 500 mg of naproxen twice a day decreases its incidence and severity.

SOURCE: Kirshner JJ, et al. Prevention of pegfilgrastim-induced bone pain: A phase III double-blind placebo-controlled randomized clinical trial of the University of Rochester Cancer Center Clinical Community Oncology Program Research Base. *J Clin Oncol* 2012;30:1974-1979.

Five hundred ten cancer patients (nonmyeloid) at 17 community-based sites were enrolled in the study; 257 received naproxen and 253 placebo. The majority were white (89%) women (86%) with breast cancer (67%). Their mean age was 56.2 years, and only 27% had received previous chemotherapy. Patients with a history of gastrointestinal bleeding or ulcers, recent heart surgery, elevated serum creatinine, and those taking nonsteroidal anti-inflammatory drugs (NSAIDs) or therapeutic doses of aspirin or warfarin were excluded from the study.

The patients were randomly assigned to take 500 mg of naproxen (n = 257) or placebo (n = 253) before their first dose of pegfilgrastim, and then twice a day (with food) for 5 days (up to 8 days if they were still experiencing pain). The pegfilgrastim was given on day 2, 3, or 4 of the chemotherapy cycle. In this double-blind study, both groups of patients filled out pain questionnaires and recorded the severity (0 to 10) and duration of their pain before and for 5 days after they received pegfilgrastim.

Pain reached its peak at 3 days post-pegfilgrastim in both groups, but it was less intense (mean 5 day AUC 6.04 vs 7.71; $P = 0.037$) and of shorter duration (1.92 vs 2.40 days; $P = 0.009$) in the patients who took naproxen. Naproxen also decreased overall pain incidence from 71.3% to 61.1% ($P = 0.020$), and severe pain (> 5/10) from 27.0% to 19.2% ($P = 0.048$).

COMMENTARY

That granulocyte colony-stimulating factors (GCSFs) cause bone pain is no surprise to practicing oncologists. That so many of our patients (almost three quarters!) suffer this side effect may, however, come as a shock. Sensitizing oncologists to this fact may be even more important than Kirshner's report that taking naproxen 500 mg twice a day for 5 to 8 days reduced the incidence of pain by 10% (severe pain by 8%), the intensity of pain by 22%, and the duration of pain by half a day. Even with this preventive regimen, just over 60% of patients still experienced pain, and almost 20% reported that the pain was severe. Clearly, new strategies are needed to prevent and treat this too often debilitating side effect of what has become an essential component of many chemotherapy regimens.

Clinical trial data support the use of primary prophylactic GCSFs when the risk of febrile neutropenia is in the range of 20% or higher.[1]

Although most commonly used regimens have a risk less than this, an increasing number fall into this category, especially the dose-dense regimens that have proven so effective in the adjuvant treatment of breast cancer (the overwhelming majority of the patients in the Kirshner study).

Older adults (a group that was not well represented in Kirshner's study) comprise another growing group of cancer patients in whom the use of GCSFs is of critical importance. The risk of myelosuppression increases significantly by age 65, and primary prophylaxis with GCSF is now recognized as an important adjunct to chemotherapy in this population.[1,2] Studies have repeatedly shown that non-frail older patients benefit from and are able to tolerate commonly used chemotherapy regimens as well as younger patients, especially when adequate supportive care is provided.[3] As in their younger counterparts, dose reductions significantly compromise chemotherapy, and the use of GCSF in these circumstances increases efficacy as well as decreases morbidity.

Although 49 of the original 510 patients dropped out of Kirshner's study (equally split between the two groups), none appeared to have done so because of pegfilgrastim-induced bone pain. However, given the prevalence of significant bone pain in patients receiving pegfilgrastim, it is likely that there are those in day-to-day practice who just cannot tolerate the regimen and choose to either discontinue treatment or opt for compromised doses over pegfilgrastim-based regimens. This may be particularly true in older individuals who often have unacceptable side effects (lethargy, confusion, falls, constipation) from opioid analgesic medications. Even if they choose to "tough it out" without the stronger pain relievers, the impact of this pain on quality of life may be profound for both older and younger patients.

Amgen's official website[4] informs patients that: "The most common side effect you may experience is aching in the bones and muscles. If this happens, it can usually be relieved with a nonaspirin pain reliever, such as acetaminophen." Unfortunately, there are no studies to confirm this, and, given the number of patients in Kirshner's study who still had bone pain after naproxen prophylaxis, it seems unlikely that acetaminophen will do any better. If it did, it would certainly be less toxic.

Though the design of Kirshner's study had many strengths, it did not provide adequate information about the well-known side effects of naproxen. Gastrointestinal and renal toxicity from NSAIDs are relatively common (especially in older patients), but they usually take some time to develop. NSAID-related side effects were not seen in Kirshner's study, but the patients were only asked about serious adverse events during the first cycle of chemotherapy. It would be wrong (perhaps even dangerous) to generalize the absence of these side effects to standard care where patients are given multiple cycles of chemotherapy over many months. Since most of the patients in this study were relatively young, healthy, white women with breast cancer, it is also difficult to extrapolate these findings to other cancer diagnoses and patient groups.

Nevertheless, this study does provide good evidence that naproxen may be useful in diminishing the impact of pegfilgrastim-induced bone pain in some patients. Until we understand more about its toxicity over the entire course of chemotherapy, it should be used judiciously in only selected patients. Since the majority of cancer chemotherapy patients receiving GCSFs will have significant bone pain, oncologists should pay particular attention to the published guidelines, and, when they do use GCSFs, assess and treat pain proactively and aggressively. ■

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ILLUSTRATIVE CASE SERIES

Monoclonal Gammopathy of Undetermined Significance

By William B. Ershler, MD

A 64-year-old commercial airline pilot was seen by his primary physician because of a bothersome, non-productive cough. He has a history of asthma but requires no medications other than occasional albuterol inhalation. Physical examination was unremarkable, as were the

complete blood count and chest x-ray. However, the serum chemistry revealed an elevated total serum protein of 8.9 g/dL with a normal albumin of 3.8 g/dL. Serum electrolytes, creatinine, blood urea nitrogen, and calcium were within normal limits. A serum protein electrophoresis was obtained and this revealed a monoclonal spike of 1.9 g/dL. Immunoelectropheresis demonstrated the presence of a monoclonal IgA/λ. The patient was referred for opinion regarding diagnosis and management.

DISCUSSION

This patient presented with an unrelated problem but was discovered to have an elevated serum protein and a monoclonal immunoglobulin, suggesting the likely diagnosis of monoclonal gammopathy of undetermined significance. To confirm this and to be certain that criteria for myeloma or the intermediate smoldering multiple myeloma (SMM) are not met, bone x-rays should be obtained and bone marrow sampled.

Table 1: Myeloma Precursors

	MGUS	SMM
Serum M protein	<3 g/dL	>3 g/dL
Clonal bone marrow plasma cells	<10%	>10%
End organ damage	None	None
Prevalence in general population	3-5%	Unknown
Risk of progression to MM, lifelong	1%/year	10%/year

If monoclonal gammopathy of undetermined significance (MGUS) criteria are met, we would advise quarterly visits at a minimum to assess the stability of his plasma cell dyscrasia. Here, interval history, physical exam, CBC, chemistry panel (including creatinine, total protein, and calcium), and measurement of the monoclonal (M) protein, either by serum protein electrophoresis or quantitative IgA level would be catalogued.

Not all patients will require quarterly visits but the presence of certain risk factors for myeloma development (IgA isotype, > 1.5 g/dL M protein, discussed below) would warrant active surveillance. If he were to demonstrate progression to SMM within a year or less, one might be tempted to consider introducing definitive myeloma therapy at that time, acknowledging that there is little trial-based evidence on which to base this recommendation. However, in light of his relatively young age and absence of comomorbidity, this may well be the optimal time to provide aggressive cytoreductive therapy. Such, however, is currently not the standard approach, and if treatment is to be introduced it would be best to consider enrolling in a clinical trial. There are several ongoing trials for treatment of MGUS, and particularly SMM, and the reader is directed to a recent comprehensive review written by Korde and colleagues,[1] which includes a listing of completed and ongoing interventional studies. Despite the sense that early treatment would be advantageous, published reports to date have not been convincing with regard to an impact on overall survival, although progression-free survival and decreased skeletal events have been observed in selected studies. Furthermore, there is now heightened concern about the occurrence of second malignancies in treated myeloma patients,[2] and this may be particularly germane for those with a projected long treatment course. Thus, the standard of care remains continued surveillance for patients with MGUS SMM and intervention only when criteria for multiple myeloma are established.

RISK STRATIFICATION

In earlier days, the demonstration of a monoclonal protein in this setting (asymptomatic, otherwise healthy patient) was often considered an incidental finding[3] — the so-called "benign monoclonal gammopathy," particularly when it occurred in older patients. Although it has long been recognized that some patients with this disorder go on to develop multiple myeloma,[4] this had been considered the exception rather than the rule. However, it became clear by the mid-1970s that the finding was associated with a significantly higher risk for developing multiple myeloma, Waldenstrom macroglobulinemia, amyloidosis, and other related disorders. Accordingly, in 1978, Kyle proposed the term MGUS be substituted for benign monoclonal gammopathy.[5] In a comprehensive analysis of Mayo Clinic patients with MGUS, certain risk factors for progression to myeloma were identified, and a stratification model established (*see Table 2*). The identified risk factors are: 1) M protein level > 1.5 g/dL; 2) non-IgG M component (e.g., IgA); and, 3) abnormal serum free light chain ratio. That same Mayo group published a report[6] including

Table 2: Mayo Clinic MGUS Risk Stratification[6]

Number of risk factors	20-year progression, %	Relative risk (RR)
0	5	1
1	21	5.4
2	37	10.1
3	58	20.8

more than 1000 MGUS patients demonstrating the 20-year progression to myeloma increased incrementally with the number of risk factors present (*see Table 2*). Thus, for all MGUS patients, the risk is approximately 1% per year, but more than half of those with all three risk factors will develop myeloma over the same time span.

Thus, MGUS and SMM are now considered precursors of plasma cell malignancy. It is likely that most, if not all, patients with the diagnosis of multiple myeloma had prior MGUS, albeit of varying duration. With the prevalence of MGUS approaching 5% in the 50 years and older population, and with expanding life expectancy with the median survival for those who are currently 50 years old approximately 35 additional years, it is very likely that the coming decades will see strikingly more myeloma patients, particularly in those 75 years and older. ■

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ABSTRACT & COMMENTARY

Diabetes as a Risk Factor for Hematologic Malignancy

By William B. Ershler, MD

SYNOPSIS: In a meta-analysis of current observational (both case-control and prospective cohort) studies evaluating the potential association between type 2 diabetes mellitus and the incidence of hematological malignancy, an increased risk for non-Hodgkin lymphoma and leukemia was demonstrated as well as a trend toward an increased risk for myeloma. Confounding factors such as age, obesity, smoking, and alcohol (risks for both diabetes and malignancy) could not be completely accounted for in such an analysis. However, certain potential mechanisms, such as increased inflammatory cytokines and over expression of insulin-like growth factor, known features of diabetes, may also be of importance in the development of certain hematological malignancies, and warrant investigation.

SOURCE: Castillo JJ, et al. Increased incidence of non-Hodgkin lymphoma and myeloma in patients with diabetes mellitus type 2: A meta-analysis of observational studies. *Blood* 2012;119:4845-4850.

Although there have been prior reports of an association of certain hematological malignancies with diabetes mellitus, including a meta-analysis from this same group,[1] a clear association has not been definitively established, particularly for certain types of hematologic malignancy. To address this, Castillo and colleagues conducted a second meta-analysis including additional studies published since their prior report. Articles were included in this analysis if they contained original data from epidemiologic observational studies (cohort or case-control) examining potential association between type 2 diabetes mellitus (DM2) and the incidence of lymphoma, leukemia, or myeloma over a minimum follow-up of 3 years. The quality of included studies was determined using the Newcastle-Ottawa Scale.[2] There were 26 studies identified (13 case-control and 13 cohort studies) evaluating the association of DM2 with one or more hematological malignancy. The meta-analysis was performed using standard methodology[3] with random-effect modeling[4] with specific attention to account for publication bias.[5]

Outcome was calculated as odds ratio (OR) for a specific hematological malignancy occurring in patients with DM2. The OR for non-Hodgkin lymphoma (NHL) was increased at 1.22 (95% confidence interval [CI] 1.07-1.39; $P < 0.01$) but the OR for Hodgkin lymphoma was not. There was an increased OR for peripheral T-cell lymphoma (OR 2.42, 95% CI 1.24-4.72; $P = 0.009$) but not for other NHL subtypes. The OR for leukemia was 1.22 (95% CI 1.03-1.44; $P = 0.02$), and the OR for myeloma was 1.22 (95% CI 0.98-1.53; $P = 0.08$).

COMMENTARY

Thus, this analysis demonstrated that patients with DM2 have a mild-to-moderate increased risk of developing NHL, particularly peripheral T-cell lympmhoma (PTCL), but, curiously, not Hodgkin lymphoma. Furthermore, the odds for developing leukemia were increased, but the power of the study

was insufficient to identify whether the risk pertained to acute or chronic, or for that matter lymphoid or myeloid variants. Further, the risk for myeloma was apparent, but did not quite reach a level of statistical significance.

Epidemiologic studies are famous for identifying interesting and potentially important associations. Thus, it appears the presence of type 2 diabetes renders an increased risk for certain hematologic malignancies. The authors point to a joint consensus statement from the American Diabetes Association and the American Cancer Society[6] in which several features of DM2 are mentioned as potential pathways to hematologic malignancy, including inflammation, hyperinsulinemia, increased insulin-like growth factor (IGF), and up-regulation of the IGF-1 receptor. To complicate things, there are a number of factors that are risks for both DM2 and neoplasia (including hematologic malignancy) such as advancing age, obesity, smoking, and alcohol.

Diabetes is very common, especially with advancing age, and with the shifting demographic in the United States and elsewhere, in-depth studies that identify the mechanisms of this association would be of great value, particularly if the causative factors can be modified and the risk for hematological malignancy thereby reduced. ■

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CME Questions

1. Regarding the benefits of aspirin in terms of cancer prevention, which of the following is *true*?

a. Case-control studies show no benefit of aspirin with regard to cancer occurrence, whereas randomized controlled trials generally do reveal benefit.
b. Case-control studies do not reflect the same magnitude of benefit as randomized controlled trials.
c. Case-control studies indicate a significantly greater benefit of aspirin when compared with randomized controlled trials.
d. There is general agreement with regard to the benefit of aspirin in prevention of cancer when data from case-control studies are compared with randomized controlled trials.

2. Which of the following statements regarding the nonuse of aspirin and statins published by Zaorsky et al is *true*?

a. Men who use statins are at an increased risk of biochemical failure when treated with radiation therapy for their prostate cancer.
b. Men who use aspirin are at an increased risk of biochemical failure when treated with radiation therapy for their prostate cancer.
c. Men who use aspirin are at a decreased risk of biochemical failure when treated with radiation therapy for their prostate cancer..
d. Men who use statins are at a decreased risk of biochemical failure when treated with radiation therapy for their prostate cancer
e. Both a and b
f. Both c and d

3. Which statement about pegfilgrastim-induced bone pain is *false*?

a. Most chemotherapy patients receiving pegfilgrastim experience bone pain.
b. Naproxen may be useful in preventing pegfilgrastim-induced bone pain.
c. The best course of action is to discontinue pegfilgrastim and decrease the dose of chemotherapy.
d. All of the above

4. A 60-year-old man diagnosed with monoclonal gammopathy of undetermined significance has what chance of developing multiple myeloma by the age of 85 years?

a. 1 in 100
b. 1 in 50
c. 1 in 25
d. 1 in 4

5. In the recent meta-analysis, type 2 diabetes was found *not* to be associated with increased risk for the development of:

a. Hodgkin lymphoma.
b. non-Hodgkin lymphoma.
c. peripheral T-cell lymphoma.
d. leukemia (not otherwise specified).
e. None of the above

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Does Azithromycin Cause Cardiovascular Death?

In this issue: Azithromycin and cardiac risk; warfarin and heart failure; aspirin and VTE; effectiveness of long-acting contraceptives; and FDA actions.

New study finds increased risk

Is azithromycin proarrhythmic? Macrolide antibiotics are associated with an increased risk of sudden cardiac death, but azithromycin (Zithromax), the popular "Z pack" macrolide, has been considered safe. That may change based on the results of a new study from Vanderbilt. Researchers reviewed the records of patients in the Tennessee Medicaid cohort to detect an increased risk of death related to short-term cardiac effects of azithromycin and several control antibiotics. Patients with serious noncardiovascular illness and hospitalized patients were excluded. Over the study period, there were almost 350,000 patients who took azithromycin, 1.35 million patients who took amoxicillin, 265,000 patients who took ciprofloxacin, nearly 200,000 patients who took levofloxacin, and nearly 1.4 million control patients. Five days of therapy with azithromycin compared to no antibiotics significantly increased the risk of cardiovascular death (hazard ratio [HR] 2.88, confidence interval [CI], 1.79 to 4.63; $P < 0.001$) and death from any cause (HR 1.85; 95% CI, 1.25 to 2.75; $P = 0.002$). Use of amoxicillin was not associated with increased risk of death. Relative to amoxicillin patients, patients taking azithromycin were at 2.5 times higher risk of cardiovascular death and 2 times higher risk of death from any cause, although the absolute risk was low with an estimated 47 additional cardiovascular deaths per million courses. Patients at risk for cardiovascular disease were at higher risk, with an estimated 245 additional cardiovascular deaths per 1 million courses. Cardiovascular death risk was higher with azithromycin compared to ciprofloxacin, but the death rate from levofloxacin was roughly the same. The authors conclude that 5 days of azithromycin was associated with a small but absolute increased risk of cardiovascular death, which was most pronounced in patients with a high baseline risk for cardiovascular disease (*N Engl J Med* 2012;366:1881-1890). Soon after this study was published, the FDA issued a statement urging patients to continue taking azithromycin unless instructed otherwise by their health care professional. The FDA will review the results of the study and will communicate any new information on azithromycin, including the potential risk of QT interval prolongation, to health care professionals and the public. Health care professionals are urged to report any adverse effects related to the use of azithromycin to the FDA's MedWatch Safety program. ■

Warfarin doesn't prevent death

Warfarin is no more effective than aspirin in preventing mortality in patients with heart failure who are not in atrial fibrillation (AF), according to a new study. More than 2300 patients with a left ventricular ejection fraction less than 35% (average 25%) and a mean age of 61 years were randomized to warfarin with a target INR of 2.0-3.5 or

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) 262-5404. E-mail: neill.kimball@ahcmedia.com.

aspirin 325 mg per day. The primary outcome was ischemic stroke, intracerebral hemorrhage, or death from any cause. Patients were followed for up to 6 years with a mean follow-up of 3.5 years. There was no difference in the primary outcome (7.47 events per 100 patient years for warfarin, 7.93 for aspirin; HR with warfarin 0.93, CI, 0.79 to 1.10, $P = 0.40$). Warfarin was associated with a significant reduction in the rate of ischemic stroke but was associated with a higher rate of hemorrhage. The authors conclude that among patients with heart failure who are in sinus rhythm, there was no difference in outcome between warfarin and aspirin, but note that since warfarin was associated with a lower risk of ischemic stroke, the choice between the two drugs should be individualized (*N Engl J Med* 2012;366:1859-1869). An accompanying editorial asks, "Could there be some patients with heart failure who would benefit from warfarin?" Those with AF, a history of cardioembolic stroke, history of left ventricular thrombus, and perhaps those with atherothrombotic coronary artery disease may benefit, but in general, warfarin cannot be recommended for patients with heart failure who are not in AF (*N Engl J Med* 2012;366:1936-1938). ■

Aspirin and venous thromboembolism

Aspirin may be protective in patients who have had an unprovoked venous thromboembolism (VTE) to prevent recurrence after they finish oral anticoagulant therapy. In a double-blind study, patients with first-ever unprovoked VTE who had completed 6-18 months of oral anticoagulant treatment were randomly assigned to aspirin 100 mg daily or placebo for 2 years. The primary endpoint was recurrent VTE with major bleeding being the primary safety outcome. Recurrent VTE occurred in 6.6% of patients on aspirin and 11.2% of patients on placebo (HR 0.58; 95% CI, 0.36 to 0.93). One patient in each group had a major bleeding episode. The authors conclude that aspirin reduces the risk of recurrence in patients with unprovoked VTE after they have finished anticoagulant therapy, with no apparent increase in risk of major bleeding (*N Engl J Med* 2012;366:1959-1967). This study is important because about 20% of patients with unprovoked VTE have a recurrence within 2 years. It also shows that taking low-dose aspirin safely reduces that risk by nearly half. An accompanying editorial points out that a similar but larger study is currently ongoing in Australia and New Zealand with results due later this year (*N Engl J Med* 2012;366:2028-2030). ■

Long-acting contraceptives are better

Long-acting contraceptives, such as IUDs and implants, are up to 20 times more effective than oral contraceptives and other short-acting contraceptive methods, according to a new study. In a large, prospective cohort study, women participants were provided with the reversible contraception of their choice at no cost for 3 years. The endpoint was failure of long-acting reversible contraception (IUDs and implants) compared with commonly prescribed contraceptive methods, including oral contraceptive pills, transdermal patches, contraceptive vaginal rings, and depot medroxyprogesterone acetate injection (DMPA). In the nearly 7500 women participants, there were 334 unintended pregnancies. The failure rate among participants who used pills, patch, or ring was 4.55 per 100 participants years as compared with 0.27 among participants using long-acting reversible contraception (HR after adjustment for age, educational level, and history with respect to unintended pregnancy 21.8; 95% CI, 13.7 to 34.9). The rate for DMPA was also low at 0.22. Younger women (< 21 years) who used a short-acting contraceptive had a pregnancy rate almost twice as high as older participants. The pregnancy rate among women who used DMPA, an IUD, or implant were similarly low regardless of age. The authors conclude that the effectiveness of long-acting reversible contraception is superior to that of contraceptive pills, patch, or ring and is not altered in adolescents or young woman (*N Engl J Med* 2012;366:1998-2007). This study not only points out the reliability of long-acting contraceptives, but also the surprisingly high failure rate of short-acting contaceptives, especially in young women. ■

FDA actions

In the biggest generic launch since last year's atorvastatin (Lipitor), the FDA has approved generic clopidogrel (Plavix). The popular antiplatelet drug, with sales of more than $9 billion last year, will be available from seven generic manufacturers in the 75 mg strength and four manufacturers in the 300 mg strengths. The immediate "multisource" status of the generic approval should result in dramatic cost reductions for patients, from an average of $200 per month to about $40 per month. The drug is approved for treatment of acute coronary syndrome and prevention of thrombotic events in patients who have had a recent myocardial infarction, recent stroke, or peripheral artery disease. ■

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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Lose-Dose Abdominal CT for Appendicitis

Source: Kim K, et al. *N Engl J Med* 2012; 366:1596-1605.

RADIATION EXPOSURE FROM CT IS QUITE substantial. A "typical" abdominal CT (AB-CT) examination exposes a patient to X-radiation equivalent to more than 500 chest X-rays. The dose-response relationship between diagnostic/therapeutic radiation and untoward consequences is uncertain; nonetheless, the magnitude of radiation from imaging — combined with the ever-increasing frequency with which high-dose diagnostic imaging is used — prompts concern. Perspicacity for wise use of radiation is imperative, especially in younger persons, in whom the lag time for adverse impact of radiation is most pertinent and in whom the likelihood of additional radiation exposure is increased.

When appendicitis is suspected, AB-CT has become the diagnostic imaging of choice. Standard-dose AB-CT exposes the patient to approximately 500 mGy/cm of radiation. Low-dose AB-CT exposes the patient to approximately 100 mGy/cm, but it is not widely used because of uncertainty about its accuracy (compared to standard AB-CT).

Kim et al randomized young adult patients with suspected appendicitis (n = 891) to low-dose or standard-dose AB-CT. The primary outcome of the study was the number of appendectomies performed that did *not* demonstrate appendicitis.

The negative appendectomy rate did not differ significantly between the two groups (3.2% vs 3.5%). Statistical criteria were satisfied that low-dose AB-CT is noninferior to standard dose AB-CT. Clinicians may wish to ascertain the radiation dose used in AB-CT for appendicitis at their institutions. ■

Degludec, a New Ultra-long-acting Basal Insulin for Diabetes

Source: Garber AJ, et al. *Lancet* 2012; 379:1498-1507.

THE ADVENT OF BASAL INSULINS THAT DO not have a prominent peak plasma level — so-called "flat" pharmacodynamic activity — was a welcome addition to diabetes management, since their predecessor, NPH, was often limited by problematic hypoglycemia. Utilization of glargine and detemir insulins, the two basal insulin analogs most recently available in the United States, has mushroomed in response to their superior tolerability compared to NPH insulin: a reduction of about 20% in hypoglycemic episodes and less weight gain. Degludec has recently been submitted to the FDA for approval. It is considered an ultra-long-acting basal insulin.

Garber et al performed a controlled trial in type 2 diabetic patients (n = 972) to compare degludec with glargine as part of a basal-bolus regimen. The primary endpoint of the trial was achieved A1c, but rates of hypoglycemia were also compared.

Both insulins achieved similar A1c improvement, and the overall rate of hypoglycemia was low in both groups. However, the degludec patients experienced almost 20% fewer hypoglycemic episodes (defined as glucose < 56 mg/dL) than the glargine group.

Degludec insulin, if FDA approved, may provide a superior hypoglycemia risk profile than insulin glargine while achieving a similar level of A1c reduction. ■

Prevention Benefits of Aspirin: Cancer, Vascular, or Both?

Source: Rothwell PM, et al. *Lancet* 2012; 379:1602-1612.

AMERICAN CLINICIANS HAVE TYPICALLY thought of aspirin as a preventive (primary and secondary prevention) for cardiovascular (CV) events. Recently, the role of aspirin for primary prevention of CV events has been embattled because although clinical trial data indicate reduction in CV events, total mortality has not been convincingly favorably impacted.

Aspirin appears to have at least two favorable effects upon cancer. It appears to decrease the incidence of colon cancer, and — as a consequence of what otherwise might appear to be an adverse effect — enhances detection rates of existing colon cancer by increasing their proclivity to bleed.

Rothwell et al performed an analysis of trial data from 51 randomized, controlled aspirin prevention trials. Among almost 70,000 participants, risk of cancer death was reduced by approximately 15%, and incidence of cancer was reduced by about one-fourth. Although there is a reduction in vascular events with the use of aspirin, bleeding events induced by aspirin tend to balance this out in the earliest years of aspirin use.

Since cancer is well-entrenched as the No. 2 cause of death in America (and is inching into the No. 1 slot), when we think of the preventive benefits of aspirin, it is time to reframe our thinking into appreciation of the combined benefits of cancer mortality reduction in addition to CV event reduction. ■

UTI in Long-Term Care Facilities Among Older Adults

Source: Genao L, Buhr GT. *Ann Long-Term Care: Clin Care Aging* 2012;20:33-38.

UNLESS A DRAMATIC DEMOGRAPHIC SHIFT occurs, approximately one in four of us will reside in a long-term care facility (LTCF) during our lifetime. Among LTCF residents, 30-50% of antibiotic utilization is for urinary tract infections (UTIs), resulting in substantial expense, adverse drug reactions, and ever-growing populations of resistant bacteria.

The first guidelines for managing UTI in LTCF were issued in 1991. The McGeer criteria included fever, chills, dysuria, frequency, urgency, flank pain, suprapubic pain, change in urine character, worsening of mental or functional status, and new or increased incontinence. Unfortunately, these criteria (and their subsequent modification, known as the Loeb guidelines) had a sensitivity of only 30%, a positive-predictive value of 57%, and negative-predictive value of 61%. Further modifications of the Loeb guidelines have evolved into an algorithm with major and minor symptoms that have been shown to reduce false-positive diagnoses by 30% and antibiotic use by 20%.

Genao and Buhr do not support treatment of asymptomatic bacteriuria in the LTCF setting for older adults. They remind us of the merit of urine dipstick testing because of its strong negative-predictive value: A dipstick urine test negative for leukocyte esterase and nitrate has an essentially 100% negative-predictive value for the presence of UTI. Although not yet in widespread use, other biomarkers of bacterial infection are gaining support. For instance, serum procalcitonin has been studied as a marker of bacterial infection (including UTI) in young adults, and might perform equally well in older adults. ■

Beyond Glucocentricity: Nonglycemic Effects of Incretin-Based Therapy

Source: Brown NJ. *J Am Soc Hypertens* 2012;6:163-168.

ALTHOUGH GLUCOSE CONTROL IN DIABETES has been consistently demonstrated to improve microvascular outcomes, no randomized clinical trial has shown favorable effects on macrovascular disease (stroke, MI, overall mortality). Whether the failure to achieve macrovascular risk reduction is secondary to adverse effects like weight gain, hypoglycemia, catecholamine activation, or other factors remains to be determined. In the mean time, clinicians would like to use agents that have favorable effects on glucose/A1c, but — at worst — neutral effects on cardiovascular risk factors.

The incretin class of agents is currently comprised of GLP-1 agonists (e.g., exenatide, liraglutide) and DPP4 inhibitors (e.g., sitagliptin, linagliptin, saxagliptin). Although both subgroups blunt glucagon and induce glucose-dependent insulin secretion, only the GLP-1 agonists have sufficient potency to also increase satiety and slow gastric emptying. Incretins are generally weight neutral (DPP4) or associated with weight loss (GLP-1). Accordingly, favorable lipid or blood pressure effects might be associated with incretins compared to other treatments that increase weight. The DPP4 enzyme has also been shown to be responsible for breakdown of some vasoactive peptides; hence, changes in blood pressure could be a direct effect of DPP4 inhibition. Because GLP-1 enhances endothelial function, any medication that augments GLP-1 would be anticipated to at least potentially favorably effect vascular function. We look forward to incretin clinical trials that will define the cardiovascular outcomes associated with this class of therapy. ■

Home BP Monitoring May Assist BP Goal Attainment in the Elderly

Source: Cushman WC, et al. *J Am Soc Hypertens* 2012;6:210-218.

ALTHOUGH CLINIC BLOOD PRESSURE (CBP) has been the primary standard by which the majority of major clinical hypertension (HTN) trials have been measured, home BP (hBP) and ambulatory blood pressure monitoring (ABPM) correlate more closely with outcomes and target organ damage. With the advent of reliable, inexpensive, validated devices for home oscillometric BP measurement, national and international agencies now recommend routine inclusion of home BP monitoring for patients with HTN.

Cushman et al report on a trial in elderly hypertensives (men and women > age 70) which compared hBP monitoring with cBP monitoring (n = 128) over 16 weeks. They determined that hBP measurements were consistent with cBP.

Adherence to HTN medications is suboptimal. Utilization of hBP monitoring enables early detection of hypotension, facilitates dose titration (up or down), and may uncover otherwise unidentified insufficient durability of pharmacotherapy (i.e., nighttime measurements showing a waning of antihypertensive effect). As has been demonstrated in other populations, elderly patients can effectively and reproducibly use hBP, which may enhance long-term adherence. ■

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