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A monthly update of developments in cancer treatment and research

ABSTRACT & COMMENTARY

Outcomes for Patients on Long-term Imatinib Treatment for Chronic Myelogenous Leukemia

By William B. Ershler, MD

SYNOPSIS: In a multinational observational study, independent from pharmaceutical support and involving both academic and community treatment centers, long-term follow-up for chronic myelogenous leukemia (CML) patients who, after two years of imatinib therapy, were in complete cytogenetic remission was undertaken for a median of 5.8 years. Although side effects were common, only a very small percentage of patients discontinued the drug and the majority maintained their cytogenetic response. In fact, the incidence of second malignancies and overall survival were no different for the CML patients in this cohort than for the general population in Italy.

SOURCE: Gambacorti-Passerini C, et al. Multicenter independent assessment of outcomes in chronic myelogenous leukemia patients treated with imatinib. *J Natl Cancer Inst* 2011;103:553-561.

Community-derived data on long-term consequences of imatinib therapy for chronic myelogenous leukemia (CML) have been lacking. To provide this, a multinational, pharmaceutical-independent observational study (the Imatinib Long-Term Side Effects [ILTE] study) was conducted. This study, supported by Italian public funds, included 27 active centers located on five continents.

Consecutive CML patients (n = 832) who were treated with imatinib before 2005 and who were in complete cytogenetic remission (CCyR) after 2 years (± 3 months) of treatment were enrolled. Of the 832 patients, imatinib was the first-line treatment in 354 and was second-line in 478. The majority (89.5%) of those treated as second-line had received initial treatment with interferon, and for them the imatinib was started a median of 1.7 years after the initial diagnosis of CML.

For this study, the observation period began after 2 years of imatinib treatment and only patients in CCyR were enrolled. The incidence of the first serious and/or non-serious adverse event and the loss of CCyR were estimated according to the Kaplan–Meier method and compared by the standard log-rank test. Attainment of negative Philadelphia chromosome hematopoiesis was assessed with cytogenetics and quantitative

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Clinical Oncology [ALERT]

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polymerase chain reaction (PCR). Cumulative incidence of death related or unrelated to CML progression was estimated, accounting for competing risks, according to the Kalbleisch–Prentice method.

At the time of analysis, the median duration of imatinib treatment was 5.8 years. There were 139 recorded serious adverse events, of which 19.4% were considered imatinib-related. A total of 830 non-serious adverse events were observed in 53% of patients, and of these, 560 (68%) were considered imatinib-related. The most frequent were muscle cramps, asthenia, edema, skin fragility, diarrhea, tendon, or ligament lesions. Nineteen patients (2.3%) discontinued imatinib because of drug-related toxic effects. Forty-five patients lost CCyR, at a rate of 1.4 per 100 person-years. Durable (> 1 year) negative Philadelphia chromosome hematopoiesis was attained by 179 patients. Twenty deaths were observed, with a 4.8% mortality incidence rate (standardized incidence ratio = 0.7; 95% confidence interval = 0.40 to 1.10, P = 0.08), and only six of the 20 deaths were associated with CML progression.

When compared to the general Italian public, the age-adjusted death rate for patients who were in CCyR after 24 months of imatinib treatment was not different. Also of importance, the development of non-CML malignancy in this cohort was no different than the expected incidence in the general population.

COMMENTARY

Imatinib treatment for CML remains the single best example of effective targeted therapy, and its introduction in the late 1990s has dramatically changed the long-term outcome for patients with this disease. The current report, observational by design, provides additional confidence in the success of such treatment. For patients who remain in CCyR after 2 years of imatinib, survival appears no different than the general population, despite the fact that, at least in this cohort, major molecular remission, determined by PCR was apparent in just less than 25%. Yet, the annual loss of CCyR was low (only 45 of the 832 patients over the years of the study). Nonetheless, more than half of the patients had some adverse effects and some of these were clearly sufficient to alter quality of life.

In this group of patients, more than 50% had received prior interferon treatment and it is notable that there was no difference in the durability of CCyR for these patients when compared to those who had received imatinib as first treatment. Earlier reports had indicated that patients with prior exposure to interferon were more likely to reach a durable molecular response;[1,2] however, more recent reports have raised questions regarding this conclusion.[3]

Recently, second-generation tyrosine kinase inhibitors (nilotinib and dasatinib) have produced superior molecular responses when compared to imatinib in Phase 3 trials,[4,5] such that the FDA has now approved their use as first-line treatment for chronic phase CML. Yet, long-term outcome data, particularly with regard to side effects, second malignancy, and even durability of response, are not available. Thus, because of the long-term experience with imatinib, such as that provided by the ILTE study, it is quite reasonable to continue with this agent as first line, as was indicated as the personal preference of Douglas Smith in his editorial accompanying the publication of the ILTE study.[6] ■

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ABSTRACT & COMMENTARY

Transplant vs Imatinib for Accelerated Phase CML

By Andrew S. Artz, MD, MS

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

SYNOPSIS: Limited data are available to guide the decision between up-front allogeneic hematopoietic cell transplantation (HCT) or imatinib on long-term outcomes for accelerated phase chronic myelogenous leukemia (CML). Outcomes of CML accelerated phase patients likely transplant-eligible based on age under 60 years and good health were analyzed. Of these, 87 patients elected to receive long-term imatinib and 45 patients decided on initial HCT. HCT patients typically received imatinib or other therapy for 3 months in preparation for HCT. Overall survival (OS) was superior for HCT ($P = 0.023$). A CML risk score was generated based on CML duration 12 months or more, hemoglobin < 10.0 g/dL, and 5% or more peripheral blasts. For low-risk patients, event-free survival (EFS) and OS for both cohorts exceeded 80%. For intermediate risk patients, higher EFS and OS for HCT were not statistically different compared to imatinib. For higher-risk patients, EFS and OS favored HCT. Specifically, five-year survival for HCT was 100% vs 17.7% with imatinib ($P = 0.008$). These data support early HCT for high-risk accelerated phase CML and warrant consideration for intermediate risk patients.

SOURCE: Jiang Q, et al. Imatinib mesylate versus allogeneic hematopoietic stem cell transplantation for patients with chronic myelogenous leukemia in the accelerated phase. *Blood* 2011;117:3025-3031.

Chronic myelogenous leukemia (CML) has classically been described as a triphasic disease with patients presenting in chronic phase, progressing to accelerated phase, and eventually terminating in blasts crisis. Around 10%-15% initially will present past chronic phase. The curative potential of allogeneic hematopoietic cell transplantation (HCT) and the lack of other effective therapies placed HCT as the recommended treatment for eligible patients. A particular potent graft-versus-leukemia occurs in CML promoting long-term disease control.[1] The short- and long-term morbidity and mortality of HCT raises concerns even for transplant-eligible patients. The advent of imatinib mesylate (Gleevec), an oral inhibitor of BCR/ABL tyrosine kinase activity, revolutionized treatment by enabling cytogenetic remissions in around 80% of patients in chronic phase with excellent tolerance.[2] Response rates and response durability decline markedly for more advanced disease phases. Imatinib at 600 mg daily induces initial hematologic control in 80% but cytogenetic remissions occur in around 20% for accelerated disease and suboptimal survival of 37 months.[3,4] For HCT candidates, the optimal timing to proceed remains uncertain. Early HCT allows definitive therapy prior to drug resistance but delayed transplant permits highly responsive patients to avoid early transplant-related morbidity and mortality.

In this retrospective review, investigators summarized records of 132 patients diagnosed with accelerated phase CML, good performance status, and age < 60 years at Peking University in Beijing, China, from 2001 to 2008. Patients were treated either with imatinib (n = 87) or HCT (n = 45) based on physician and personal choice. Imatinib dosing was 400 mg to 600 mg initially.

For the 87 imatinib-treated patients, 85% achieved a complete hematologic remission and 47% achieved a complete cytogenetic remission. The 6-year overall survival rate was 51.4% and median overall survival was 80 months. Seven patients eventually crossed over to HCT and another seven received one of the second-generation tyrosine kinase inhibitors of nilotinib or dasatinib.

HCT patients received 3 months or less of imatinib 400 mg daily in 71% or hydoxyurea combined with interferon if imatinib was unavailable. The median age of imatinib patients was 44 years, one decade older than HCT patients. The median duration of disease was considerably shorter for HCT patients at 2 months vs 17 months, suggesting HCT patients may have evolved more quickly. Transplant donors included HLA-matched siblings in 42% and 51% with HLA mismatched or haploidentical donors. HCT treated patients had superior event-free survival ($P = 0.008$) and overall survival ($P = 0.023$) compared to imatinib. In a multivariate model, treatment choice did not significantly influence survival. Treatment choice was then stratified by three prognostic groups (using prognostic factors of disease duration of 12 months, hemoglobin < 10.0 g/dL, and peripheral blasts of 5% or more). For low-risk patients (no risk factors), treatment did not influence event-free or overall survival. For intermediate-risk patients, imatinib achieved 61% long-term survival compared to 81% for HCT but was not statistically different. For high-risk patients, overall survival was 17.7% for imatinib-

treated patients and 100% for HCT (P = 0.008).

COMMENTARY

The broadening availability of therapies for CML presents an embarrassment of riches for devising treatment strategies. Advances in HCT, the historical gold-standard, continually push the age and health limits of HCT-eligible patients upward. In addition to imatinib, two second-generation tyrosine kinase inhibitors (nilotinib and dasatinib) are clinically available, with many more under study. This study on a large cohort of patients presenting with or developing accelerated phase disease prior to TKI exposure provides insights into treatment recommendations.

Patients reportedly selected the preference for imatinib or HCT, with transplant patients typically receiving a three-month course of imatinib or initial chemotherapy, presumably while donors were procured and pre-transplant testing occurred. Overall, HCT enabled superior event-free and overall survival. Specifically, imatinib-treated patients had 6-year event-free and overall survival of 39.2% and 51.4% compared to 71.8% and 83.3% for HCT in this group of transplant-eligible patients based on age 60 years or less and good performance status. Adjusted analysis provided a more mixed picture. Multivariate analysis did not show imatinib treatment choice was inferior to HCT whereas in stratified analysis, patients with high-risk disease features at the time of transplant fared considerably better with HCT, with 5-year overall survival of 100% vs 17.7% for imatinib. Intermediate risk disease showed an absolute benefit of 20% on survival but this was not statistically significant.

The major limitation in this analysis rests with retrospective nature of the study. Patients were not randomized and bias clearly may exist in either direction with HCT patients being younger and healthier (median age 10 years less) but also having worse disease features (more with short interval of CML before developing accelerated phase). The authors adjusted using a prognostic score and multivariate model but ultimately the sample size prevented robust estimates in subgroups. Another issue relates to the surprisingly good outcomes for HCT that may inflate the benefit of HCT, at least relative to registry data. We might anticipate better results since this series exclusively covered the imatinib period that permits both pre-transplant disease reduction and lower toxicity post-HCT therapy for relapse. However, 50% of patients received allografts from non-matched donors that typically drive inferior outcomes related to graft failure and high rates of graft-versus-host-disease and infection. The decision making for transplant also was only described as personal choice but other factors, such as donor availability and physician preference, affect decisions as well. A more practical limitation these days is that most accelerated phase patients have progressed from chronic phase while on imatinib therapy. Such imatinib failures with advancing disease represent a much higher risk patient for whom HCT would generally be advised. This series primarily consisted of about 80% progressing from chronic phase but who had not received imatinib therapy.

The authors ultimately propose an individualized algorithm to offer HCT to higher-risk patients. For clinical practice, one should initiate tyrosine kinase inhibitors for CML-accelerated patients. Promising data for nilotinib and dasatinib as front-line therapy for CML chronic phase will prompt more oncologists to employ these agents over imiatinib for initial therapy for accelerated phase.[5,6] For any HCT-eligible patient, a donor search should be offered or referral to a transplant center to start the donor search. For lower-risk patients based on achieving a complete hematologic response, complete cytogenetic remission, long-term outcomes have been quite good with imatinib alone.[4] For higher risk based on suboptimal response or baseline prognostic factors of anemia or other models, HCT should be entertained. Younger adults may still want to consider definitive therapy early as HCT persists as a proven modality for long-term survival and usually achieves similar results to imatinib over a 5- to 8-year period. ■

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ILLUSTRATIVE CASE SERIES

Gall Bladder Cancer

By Jerome Yates, MD

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

A 71-year-old retired police officer was admitted through the emergency room with right upper quadrant pain and low-grade fever. An ultrasound revealed gall bladder distension and calculi and he was taken to the operating room with a presumptive diagnosis of cholecystitis. Laparoscopic approach was converted to laparotomy when an inflammatory mass was discovered and a cholecystectomy was performed. At the time of surgery it was the impression that the changes were consistent with both chronic and acute cholecystitis. However, histopathology revealed an adenosquamous carcinoma within the fundus of the gall bladder with extension through the wall of the gall bladder and into adjacent liver.

Prior to the episode of abdominal pain that led to the emergency room visit he had been asymptomatic. His past medical history is essentially unremarkable. He has no known chronic illness and was taking no prescription drugs. He is a non-smoker and drinks approximately two beers a day. The physical examination (3 days post operatively) revealed him to robust and with minimal discomfort. His blood pressure was 150/90. There was no scleral icterus or palpable lymphadenopathy. The surgical site was healing nicely without evidence for infection. Laboratories revealed a normal complete blood count and serum electrolytes. Total bilirubin was normal. SGOT and ALT were mildly elevated but alkaline phosphatase was within normal limits. Chest/abdomen/pelvis CT scan revealed changes consistent with recent cholecystectomy but no evidence for residual mass or distant metastases.

CASE DISCUSSION

Although gall bladder cancer often presents at advanced stage it is not uncommon for it to be discovered as an incidental finding at the time of cholecystectomy for presumed cholecystitis. In the case presented, the general surgeon completed the cholecystectomy and it was not until pathology review that the resected mass was shown to harbor malignancy. Gall bladder tumors discovered incidentally, such as in this case, are not unusual. In fact, in one series of 435 patients with gall bladder surgery, 47% were diagnosed as an incidental finding during laparoscopic cholecystectomy.[1] Nonetheless, the management from this point forward would follow the same principles as if the cancer had been discovered by diagnostic procedures short of surgery. Clearly the greatest chance for long-term survival is the surgical excision of residual cancer, and efforts are called for to determine if resection is possible. An immediate second surgical procedure may not be well tolerated, particularly by patients with comorbidities or functional impairment, and it is reassuring to note that briefly delaying the second operative procedure is not associated with a survival deficit compared with immediate resection.[2]

[Gall bladder cancer typically exhibits aggressive patterns of growth and spread and the prognosis is not good for patients who present with stage III/IV disease.]

STAGING OF GALL BLADDER CANCER

In addition to the CT scan already obtained, further efforts should be considered to determine whether the patient would benefit from repeat laparotomy. As will be discussed below, the majority of patients for whom gall bladder cancer was discovered as an incidental finding after cholecystectomy are found to have residual disease upon repeat laparotomy. For patients who present with findings on imaging studies prior to surgery, laparoscopic staging has proven valuable in determining resectability of residual disease.[3] The role for positron emission tomography (PET) scanning has not been established, but there is some evidence that it is useful in detecting the presence of metastatic gall bladder cancer[4,5] and thus, it may prove useful in selecting appropriate candidates for re-resection.

SURGICAL MANAGEMENT

For patients with gall bladder cancer that presented as an incidental finding and with histology demonstrating invasion through the lamina propria into the muscular layer (such as in the current case in which the tumor actually penetrated into the adjacent liver [T3]), a second surgery is indicated providing there is no evidence for distant metastases.[6] Such is warranted because a large subset will have residual disease. For example, in one compiled series from six hospitals including 115 patients for whom re-resection was undertaken, pathology from the re-resection specimen noted residual/additional disease in 46.4% of patients.[7] As expected, T stage correlated with the extent of residual disease. For those with T1 disease, 0% had liver involvement and 12.5% had positive lymph nodes. In contrast, liver and lymph nodes were involved in 10.4% and 31.3% for those with T2 lesions and 31.3% and 36.4% for those with T3 lesions. In that series, attaining clear surgical margins was shown to strongly correlate with survival. In a retrospective analysis from a single institution (Memorial Sloan Kettering), 74% of patients who underwent surgical re-exploration following an incidental diagnosis of gall bladder cancer were found to have residual disease.[1]

For those who are considered to have potentially resectable disease, the operative procedure should include hepatic resection and lymphadenectomy with or without bile duct excision.[8] This is a complex and risky procedure that should only be performed by surgical oncologists with appropriate training and experience.[6]

ADJUVANT MANAGEMENT

There are insufficient data from which to define standard management in the adjuvant setting. Nonetheless, treatment with a fluoropyrimidine with or without radiation would be a reasonable approach.[6] For the patient under discussion, presuming apparent residual disease was resected at the second surgical procedure, and in light of the original pathology description of a T3 lesion, I personally would favor an aggressive adjuvant approach, acknowledging that the standard approach is yet to be established.

SUMMARY

Gall bladder cancer typically exhibits aggressive patterns of growth and spread and the prognosis is not good for patients who present with stage III/IV disease. For the patient under discussion, the critical next step is to determine the possibility for resection of residual disease. If preoperative imaging studies are negative and there is no other evidence for distant metastases, repeat laparotomy performed by an experienced hepatobiliary surgeon would offer the best chance for long-term survival. As mentioned, the decision to proceed thereafter to adjuvant treatment is a judgment call, not based on scientific evidence. In fact, if a clinical trial were available addressing the issue of adjuvant treatment in this setting and if the patient were willing to participate, I would favor that enrolment. ■

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RAPID REVIEW

Radiofrequency Ablation for Primary and Secondary Malignancy in the Lung

By William B. Ershler, MD

Patients with localized but non-resectable lung cancer generally are considered candidates for other types of therapy including external beam or stereotactic radiation therapy, chemotherapy, or percutaneous ablation. Similarly, patients who are considered to have resectable lesions but for whom surgical intervention would not be tolerated are also candidates for these

alternative approaches. Of these, percutaneous radiofrequency ablation (RFA) has been increasingly reported in the recent literature as being both effective and safe in these settings[1-6] and is the subject of this concise review.

PRINCIPLES OF RFA

RFA has been widely used for the treatment of malignancy, most notably for liver metastases from colorectal primary cancers. It is but one of a number of localized thermal ablative approaches that also include cryotherapy, laser, or microwave devices.[7] For the procedure, a conductive probe (electrode) is inserted into the tumor and high-frequency alternating current is transmitted from the tip or tips into the tumor and immediately adjacent tissue. This results in heating to temperatures greater than 60° C and subsequent coagulative necrosis. The amount of destruction is correlated with the impedance of the tissue and distance from the electrode. For the treatment of liver metastases, the RFA probe has been directed toward the lesion(s) by both image guidance (in the radiology suite) or by direct palpation or visualization in the operating room by surgeons. If there are no technical restrictions, the percutaneous approach is the least invasive, has a well-established safety profile, is repeatable, and can be performed in an outpatient setting. The best results are achieved in patients with limited disease burden, for example, those with 4 or fewer tumors measuring less than 2.5 cm in maximum dimension each for a total of 10 cm or less.[8]

In applying RFA to the lung, evaluations aimed at selecting appropriate patients are of critical importance. This would include assessing the target tumor location relative to emphysematous blebs or major vessels to avoid complications including pneumothorax or bleeding. In general, the safety of the procedure is exemplified by the recent report of its successful employment in patients with a single lung.[9] Yet, there is a distinct learning curve involved, as experience with the procedure has been shown to significantly reduce the risks of adverse outcomes including pneumothorax and need for chest tube placement.[10]

RFA FOR PRIMARY NSCLC

There is a subset of patients with potentially curable localized non-small cell lung cancer (NSCLC) that for one reason or another are not surgical candidates. The single institution (Rhode Island Hospital) 10-year experience of 79 evaluable patients who received primary RFA for NSCLC was reported recently.[3] The mean patient age was 75 years (range 45-91 years) and the mean tumor size was 2.5 cm (range 1-5.5 cm), and of these 15 were central (entirely within the inner two-thirds of the lung) and 64 were peripheral. Of the 79 patients, 19 (24%) underwent adjuvant external beam radiation and 9 (11%) underwent concomitant brachytherapy. For 45 (57%) of the patients there was no evidence of recurrence at follow-up imaging (range, 1-72 months, mean 17 months). Recurrence was seen in 34 (43%) patients (range 2-48 months; mean 14 months). The recurrence was local (at the site of RFA) in 13 (38%), intrapulmonary in 6 (18%), nodal in 6 (18%), and distant in 7 (21%). The median disease-free survival was 23 months. Of the pretreatment characteristics, tumor size and stage were statistically associated with recurrence, but sex, tumor location, and radiation treatment were not.

[Radiofrequency ablation is a thermal ablative approach used widely for liver metastases from colorectal primary cancers. Using RFA for treating metastatic lesions in the lung is controversial.]

RFA FOR METASTATIC LESIONS TO THE LUNG

The experience for treating metastatic lesions in the lung has been less well characterized and remains controversial although surgical approaches to metastatic renal carcinoma and sarcoma have met with some success.[11] There have been a few series[4,10,12] in which RFA has been applied to metastatic lesions in the lung. Certainly for patients for whom a local approach to metastatic disease is under consideration but who are not candidates for aggressive surgery, RFA may be considered. Candidates would include certain patients with slowly growing, accessible lesions.

CONCLUSION

RFA as an alternative to surgery or radiation is being actively investigated for malignancy within the lung and may become more widely used, particularly in patients who are not surgical candidates. However, much work needs to be done to refine the technique and to define who may best be served. It is clear that the technique

can be challenging, but in the hands of experienced practitioners the associated morbidity is manageable. It also remains unclear which form of ablative thermal energy will be optimal, and it may turn out that using microwave energy will be more effective, and such technology is currently under development.[13] ■

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CME Questions

For patients with CML in complete cytogenetic remission (CCyR) after 2 years of imatinib treatment and who continue on imatinib, the ILTE study has shown that:

a. the majority meet criteria for a major molecular remission.
b. approximately 50% will fall out of CCyR in the subsequent 5 years.
c. non-serious adverse events occur in over 50% of patients.
d. approximately 40% discontinue imatinib after 6 additional years, with the primary reason being toxicity.

For chronic myelogenous leukemia in accelerated phase, how does allogeneic hematopoietic cell transplant compare to imatinib for initial therapy?

a. Six-year survival of HCT is worse related to transplant mortality.
b. Higher disease risk patients appear to have the greatest benefit from HCT.
c. Transplant from partially matched donors should never be performed.
d. Imatinib rarely achieves hematologic remission in accelerated phase CML.

Of patients discovered to have gall bladder cancer as an incidental finding at the time of cholecystectomy for presumed cholecystitis, what percentage, upon re-exploration, will be found to harbor residual disease in the adjacent liver or lymph nodes?

a. 5-12%
b. 20-30%
c. 30-40%
d. 50% or more

Answers: c, b, d.

CME Objectives

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

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

[IN FUTURE ISSUES]

Improving Survival Rates by Surgical Resection of Colorectal Liver Metasteses

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Long-Term CV Effects of Intensive Glucose Lowering: The ACCORD Study

Source: Gerstein HC, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 2011;364:818-828.

THE ACTION TO CONTROL CARDIOVASCULAR risk in diabetes (ACCORD) study is really three studies in one, providing information about blood pressure, glucose, and triglyceride treatment in high-risk diabetic patients. Probably the most unsettling component of ACCORD was the early termination of the comparison of tight glucose control (attainment of an A1c < 6) with standard control (A1c 7-7.9) due to an unanticipated INCREASE in mortality associated with tight control. The glucose control arm of ACCORD was designed to go on for 5 years, but intensive glucose control was stopped at 3.5 years. Though various explanations for these results have been offered, none is wholly satisfying.

Once the increased mortality of tight control was appreciated, ALL study subjects were switched to the standard control regimen and followed to the 5-year mark. This most recent publication details outcomes of persons who originally were treated with tight control, and then were switched to standard control for the next 17 months.

Just as had been seen in the initial results of ACCORD, the group that had been assigned to tight control (even though now they had been receiving more relaxed control, and their A1c had risen 7.2%) continued to experience a statistically significant 19% greater risk for death. During Phase 2 of ACCORD, the frequency of hypoglycemia was the same between the standard control group and the group that had changed from tight to standard control; hence, although the greater frequency of hypoglycemia seen in tight control had received some focus as a culprit in inducing greater mortality, this follow-up suggests that is not the case. Why tight control is associated with increased mortality remains unknown. ■

Cysteine as a Biomarker for Sleep Apnea

Source: Cintra F, et al. Cysteine: A potential biomarker for obstructive sleep apnea. *Chest* 2011;139:246-252.

OBSTRUCTIVE SLEEP APNEA (OSA) IS CONsistently associated with cardiovascular misadventure: An increased risk for hypertension, tachycardia, cardiac arrhythmia, myocardial infarction, and stroke has been noted. OSA seems to reset the sympathetic nervous system to a higher level of activity, thus explaining some of these adversities. Tools to identify OSA are somewhat cumbersome and expensive. Were biomarkers available to identify OSA, clinicians could better reserve expensive confirmatory testing for persons with higher pre-test likelihood of disease.

Animal studies have found that sleep deprivation and hypoxia produce elevations in cysteine (CYS). Cintra et al measured CYS levels in subjects undergoing sleep studies (n = 75) and a group of matched controls (n = 75). A non-obese OSA subgroup was included to ascertain whether obesity has an impact on CYS.

CYS levels were significantly higher (15%-17%) in OSA subjects than controls ($P < 0.01$), whether obese or lean. A 6-month period of CPAP treatment resulted in a reduction of CYS levels. No pathogenetic role of CYS is known, but if further studies confirm the relationship between CYS and OSA, it may serve as a reasonable screening tool for selecting those who might benefit from sleep studies. ■

Steroid or Steroid Plus Long-Acting Beta Agonist for Mild Persistent Asthma

Source: Postma DS, et al. Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control. *Chest* 2011;139:311-318.

THE LARGEST BODY OF ASTHMATICS IS classified as mild persistent asthma, defined as daytime symptoms more than once weekly but not daily, nocturnal symptoms less than once weekly, and essentially normal lung function between exacerbations. At this stage, long-term controller medications — inhaled corticosteroids (ICS) or leukotriene inhibitors (LKT) — are suggested, reserving combination inhaled corticosteroid/long-acting beta agonist (ICS/LABA) for refractory cases or patients who progress to moderate persistent asthma and beyond. LABA monotherapy is no longer considered appropriate for asthma patients at any stage of disease.

Ciclesonide (CIC) is a novel ICS with

at least two favorable attributes: once daily dosing, and minimal hypothalamic pituitary axis perturbation at typical clinical doses. This clinical trial compared low-dose CIC with low-dose fluticasone/salmeterol in patients with mild persistent asthma (n = 657). The two co-primary endpoints were time to first severe asthma exacerbation and number of poorly controlled asthma days.

CIC alone was not superior to placebo in time to first severe asthma exacerbation, but ICS/LABA was. Other aspects of asthma control were comparable between the two regimens. Although ICS alone is advocated as appropriate initial treatment for mild persistent asthma, this comparison trial suggests that ICS/LABA provides at least one aspect of superiority. ■

Bisphosphonates and Femoral Fractures

Source: Park-Wyllie LY, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA* 2011;305:783-789.

ALTHOUGH BISPHOSPHONATES (BIS) HAVE A proven track record for reduction of osteoporotic fracture, reports of so-called "atypical" femoral fracture associated with BIS use has called for re-examination of the risk-benefit ratio of BIS. To do so, a case-control study of more than 200,000 Canadian women who had received BIS was performed. In this population, 716 atypical fractures occurred, and 9,723 typical osteoporotic fractures occurred.

BIS treatment of osteoporosis has been shown to reduce typical fractures by about one-fourth. Since typical fractures are 15-20 times more common than atypical fractures, approximately four times as many more atypical fractures than have been reported would have had to occur to make the risk-benefit ratio unfavorable. Additionally, not all atypical fractures are attributable to BIS use. Finally, the increased risk for atypical fracture was much more common in subjects who used BIS for more than 5 years.

Atypical fractures are an appropriate concern. Nonetheless, the typical fracture risk reduction far outweighs risk of atypical fracture induction. Risk for atypical fracture might be reduced by suggesting a drug holiday after 5 years of BIS use, particularly in women at the lower end of the spectrum of risk. ■

Can Antihypertensive Treatment Benefit Persons Without Hypertension?

Source: Thompson AM, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: A meta-analysis. *JAMA* 2011;305:913-922.

CLINICAL TRIAL DATA HAVE SHOWN THAT more than one-third of persons with prehypertension (130-139/86-89 mm Hg) will develop frank hypertension over a 4-year interval. Indeed, the lifetime risk of developing hypertension in the U.S. general population is approximately 90%. Although treatment of hypertension provides important risk reduction, clinicians rightfully wonder whether providing antihypertensive treatment to high-risk individuals (e.g., diabetics, persons with manifest cardiovascular disease) — at the stage of prehypertension or even before — might be beneficial.

Thompson et al performed a meta-analysis on 25 clinical trials that treated persons with prehypertension or normotension (total n = 40,395). Antihypertensive treatment classes included beta-blockers, ACE inhibitors, ARBs, calcium channel blockers, and diuretics, either alone or in combination.

Outcomes consistently favored antihypertensive treatment: The relative risk of stroke was reduced by 23%, MI by 20%, CHF by 29%, and all-cause mortality by 13%, all of which were statistically significant. These results suggest that patients at high risk of cardiovascular disease may benefit from use of antihypertensive pharmacotherapies at lower blood pressure than traditionally used as a threshold. ■

More Salt, Fewer Deaths in Diabetes: Who Would Have Thunk It?

Source: Ekinci EI, et al. Dietary salt intake and mortality in patients with type 2 diabetes. *Diabetes Care* 2011;34:703-709.

IN THE GENERAL POPULATION, THERE IS A linear and reversible relationship between salt intake and blood pressure (BP): more salt in begets higher BP, and salt restriction lowers BP. Although it is generally accepted that BP lowering through antihypertensive medications in hypertensive diabetics improves cardiovascular outcomes, whether BP reduction attainable through lifestyle measures, such as salt restriction, might produce similar improvements has not been well documented. Indeed, salt restriction has the capacity to activate neurohumoral systems that are potentially particularly detrimental to diabetics; for instance, salt restriction can activate the sympathetic nervous system and the renin-angiotensin-aldosterone system, and can reduce insulin sensitivity — each of which can be problematic — particularly for diabetics.

Ekinci et al performed a prospective cohort study on diabetics attending a single diabetes clinic (n = 638). Salt intake was ascertained by 24-hour sodium excretion at baseline and each follow-up visit for the ensuing 10-year period of observation.

After adjustment for other risk factors, the relationship between salt intake and mortality was INVERSE. Specifically, for every 100 mmol INCREASE in sodium excretion, all-cause mortality DECREASED by 28%! Arguments about salt have raged for decades; the authors point out that other previous studies (but none previously specifically in diabetics) have NOT consistently found an association between salt intake and mortality. ■

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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.*

Tiotropium for COPD — The New Standard?

In this issue: Anticholinergic drugs for COPD; pioglitazone for diabetes prevention; insulin degludec in Phase 3 trials; and FDA Actions.

Anticholinergic drugs for COPD

Should anticholinergic drugs be first-line agents for preventing exacerbations in patients with chronic obstructive pulmonary disease (COPD)? The answer may be yes, according to a new study in the *New England Journal of Medicine*. Researchers from Europe compared the anticholinergic drug tiotropium to the beta-agonist salmeterol in more than 7000 patients with moderate-to-very-severe COPD. The study was a randomized, double-blind, double-dummy, parallel-group trial in which tiotropium once a day was compared to salmeterol twice a day. The endpoint was the incidence of moderate or severe exacerbations. Over the 1-year study, tiotropium increased the time to first exacerbation compared to salmeterol (187 days vs 145 days, 17% risk reduction, hazard ratio [HR] 0.83; 95% confidence interval [CI], 0.77 to 0.90; $P < 0.001$). Tiotropium also increased the time to first severe exacerbation ($P < 0.001$), reduced the annual number of moderate or severe exacerbations (0.64 vs 0.72; $P = 0.002$), and reduced the annual number of severe exacerbations (0.09 vs 0.13; $P < 0.001$). Adverse events were similar in both groups. There were 64 deaths in the tiotropium group (1.7%) and 78 in the salmeterol group (2.1%). The authors conclude that in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations (*N Engl J Med* 2011;364:1093-1103). This is the first head-to-head study to show benefit for anticholinergics but it must be pointed out that cardiac patients were excluded from the study, and the annual exacerbation rates were lower than has been seen in other trials. The concomitant use of inhaled corticosteroids was evaluated and did not make a difference in the outcomes. The study was sponsored by Boehringer Ingelheim, the manufacturer of tiotropium (Spiriva). ■

Pioglitazone for diabetes prevention

Pioglitazone reduces the risk of development of diabetes among prediabetic patients, according to a new study. Pioglitazone was compared to placebo in a total of 600 patients with impaired glucose tolerance. After a median follow-up of 2.4 years, the annualized incident rates for type 2 diabetes were 2.1% in the pioglitazone group and 7.6% in the placebo group (HR 0.28, 95% CI, 0.16 to 0.49; $P < 0.001$). Conversion to normal glucose tolerance occurred in nearly half of the pioglitazone group and in 20% of the placebo group ($P < 0.001$) and treatment with pioglitazone was associated with significantly lower fasting glucose levels, 2-hour glucose levels, and hemoglobin A1c levels. Pioglitazone also was associated with a decrease in diastolic blood pressure (2.0 mmHg vs 0.0 placebo), reduced rates of carotid intimal-medial thickening ($P = 0.047$), and an increased level of HDL cholesterol (increase of 7.35 mg/dL vs 4.5 mg/dL; $P =$

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0.008). Pioglitazone caused greater weight gain than placebo (3.9 kg vs 0.77 kg; $P < 0.001$), as well as edema (12.9% vs 6.4%; $P = 0.007$). The authors conclude that pioglitazone reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes but was associated with significant weight gain and edema (*N Engl J Med* 2011;364:1104-1115). Thiazolidinediones have been falling out of favor in recent years for the treatment of type 2 diabetes due to association with edema and heart failure. This new industry-sponsored study suggests that pioglitazone (Actos) is more effective than metformin or lifestyle changes in preventing conversion of prediabetes to diabetes. What is unclear is the effect of these various interventions on long-term diabetic complications. ■

Insulin degludec in Phase 3 trials

Insulin degludec is an ultralong-acting insulin that is currently in Phase 3 trials. It forms soluble multihexamer assemblies after subcutaneous injection, resulting in a very long half-life of up to 40 hours. A new study suggests that it can be used three times a week, achieving blood sugar control equivalent to daily insulin glargine. In a 16-week randomized, open-label, parallel group trial, 245 type 2 diabetics aged 18-75 were randomized to insulin degludec once a day or three times a week, or insulin glargine once a day, all in combination with metformin. At the end of the study, mean hemoglobin A1c levels were similar across the treatment groups at 7.3%, 7.4%, and 7.2%, respectively. The rate of hypoglycemia was low in all three groups. The authors conclude that insulin degludec provides comparable glycemic control to insulin glargine without additional adverse events and may reduce dosing frequency due to its ultra-long action profile (*Lancet* 2011;377:924-931). The study was sponsored by its manufacturer, Novo Nordisk. ■

FDA actions

The FDA has approved the first new drug for lupus (systemic lupus erythematosus) since 1955. Belimumab is a fully human monoclonal antibody the targets human soluble B-lymphocyte receptor stimulator protein. It is indicated for the treatment of adult patients with active, autoantibody-positive lupus who are receiving standard therapy. In two pivotal studies, the drug was found to reduce disease activity compared to placebo plus standard therapy. More deaths and serious infections were reported for belimumab compared to placebo, and it does not appear to be effective in people of African or African American heritage (in whom the disease is three times more common), although more studies are needed to confirm this finding. Belimumab is marketed by GlaxoSmithKline as Benlysta.

The FDA has approved a phosphodiesterase type 4 inhibitor to reduce the number of exacerbations from severe COPD associated with chronic bronchitis. Roflumilast is a once daily oral pill that reduces excess mucus and cough. It does not appear to benefit COPD that involves primarily emphysema. The approval was based on two Phase 3 studies of more than 1500 patients. An accompanying medication guide informs patients of the potential risk of mental health problems including changes in mood, thinking, or behavior, as well as unexplained weight loss. Roflumilast is marketed by Forest Pharmaceuticals as Daliresp.

The FDA has approved a new angiotensin II receptor antagonist, the eighth introduced to the American market. Azilsartan medoxomil is approved for the treatment of hypertension in 40 mg and 80 mg once daily doses. The drug is touted as being more effective in lowering blood pressure than valsartan or olmesartan based on clinical trials. Like other angiotensin II receptor blockers, the drug will carry a box warning regarding pregnancy. Azilsartan is marketed by Takeda Pharmaceuticals as Edarbi.

Zostavax, Merck's vaccine for the prevention of shingles, has been approved for use in individuals ages 50-59. It previously was approved only for those 60 and older. The approval was based on a placebo-controlled trial of more than 20,000 individuals 50-59 years of age. The vaccine reduced the risk of developing shingles in this group by approximately 70%.

The FDA has approved ipilimumab for the treatment of late stage (metastatic) melanoma. The drug is a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen (CTLA-4). The approval was based on a single study of 676 patients with melanoma who had stopped responding to other therapies. When compared to an experimental tumor vaccine, those receiving ipilimumab lived an average of 3.5 months longer (10 months vs 6.5 months). Autoimmune reactions were common including fatigue, diarrhea, rash, endocrine deficiencies, and colitis. Severe to fatal autoimmune reactions were seen in 13% of treated patients. Ipilimumab is manufactured by Bristol-Myers Squibb and marketed as Yervoy. ■

Clinical Oncology Alert

2011 Reader Survey

In an effort ensure *Clinical Oncology Alert* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey. The results will be used to ensure you are getting the information most important to you.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write your answers to the open-ended questions in the space provided. Return the questionnaire in the enclosed postage-paid envelope by **July 1, 2011**.

In future issues of *Clinical Oncology Alert*, would you like to see more or less coverage of the following topics?

	A. more coverage	B. less coverage	C. about the same amount
1. appropriate treatment regimens	O A	O B	O C
2. quality-of-life treatments	O A	O B	O C
3. management of clinical symptoms	O A	O B	O C
4. uninsured patients	O A	O B	O C
5. new drug development	O A	O B	O C
6. breast cancer	O A	O B	O C
7. lung cancer	O A	O B	O C
8. prostate cancer	O A	O B	O C
9. cervical cancer	O A	O B	O C
10. FDA regulations	O A	O B	O C

11. What other topics would you like to see discussed in *Clinical Oncology Alert*? _____

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12. Are the articles in *Clinical Oncology Alert* newsletter written about issues of importance and concern to you?

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

13. What type of information not currently provided in *Clinical Oncology Alert* would you like to see added?

Please rate your level of satisfaction with the the items listed:

	A. excellent	B. good	C. fair	D. poor
14. monthly case study	O A	O B	O C	O D
15. Rapid Review	O A	O B	O C	O D
16. the new look of *COA*	O A	O B	O C	O D
17. quality of newsletter	O A	O B	O C	O D
18. article selections	O A	O B	O C	O D
19. timeliness	O A	O B	O C	O D
20. quality of commentary	O A	O B	O C	O D
21. clearness of abstracts	O A	O B	O C	O D
22. overall value	O A	O B	O C	O D
23. customer service	O A	O B	O C	O D

24. Please describe your work place:

○ A. private practice ○ B. hospital ○ C. government institution ○ D. research

○ E. Other_____

25. Do you benefit from having important points highlighted in the articles? ○ A. Yes ○ B. No

26. To which other publications or information sources about oncology do you subscribe?

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27. Which publication or information source do you find most useful, and why? _____

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28. Please list the top three challenges you face in your job today.

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29. What do you like most about *Clinical Oncology Alert*?

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31. Has reading *Clinical Oncology Alert* changed your clinical practice? If yes, how? _____

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