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Financial Disclosure:
Clinical Oncology Alert's Editor, William Ershler, MD, is on the speaker's bureau for Wyeth and does research for Ortho Biotech. Peer reviewer V.R. Veerapalli, MD, reports no financial relationship to this field of study.

Prognostic Value of CRP in Renal Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *C-reactive protein, an acute phase reactant, is shown to offer significant prognostic information for post nephrectomy patients with renal cell carcinoma. The value of this information will be enhanced if future studies indicate that patients with high levels are more likely to benefit from adjuvant therapy or if it turns out to be a sensitive marker of recurrent disease.*

Source: C-Reactive protein is an informative predictor of renal carcinoma-specific mortality. A European study of 313 patients. *Cancer.* 2007;110:1241-1247.

There is currently an awareness of the importance of inflammatory processes and the proliferative capacity of certain tumors. The association is quite remarkable for patients with renal cell carcinoma (RCC) in whom C-reactive protein (CRP) and erythrocyte sedimentation rate have been associated with survival.[1-3] In an effort to compare serum markers of inflammation and standard RCC-specific mortality predictors, Karakiewicz and colleagues performed a retrospective review of 313 patients who were treated by nephrectomy for renal cancer at two European centers. Life-table, Kaplan-Meier, and Cox regression analyses were utilized and data was analyzed in the context of age, gender, TNM stage, tumor size, Fuhrman grade, and histological subtype.

The overall follow-up time ranged from 0.1 to 20.8 years and of the total population, 54 (17.3%) died of RCC. The actuarial mean and median survival were 13.9 and 19.9 years respectively. By univariate analysis, CRP represented the most informative predictor of RCC-specific survival, followed by T-stage and performance status. In multivariate analysis, categorically coded CRP ($P = .003$), ECOG performance status ($P = .001$) and M stage ($P < .001$) achieved independent predictive status. Compared to patients with a baseline CRP level of 0-4 mg/dL, those with values between 4.1 and 23.0 mg/dL had a 5.2 fold increase in RCC-specific mortality, and those with values above 23 mg/dL had an 11-fold increased risk of RCC-specific mortality.

VOLUME 23 • NUMBER 11 • NOVEMBER 2007 • PAGES 81-88

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The UCLA Integrated Staging System (UISS), which predicts RCC-specific survival at 2 and 5 years is a commonly used instrument for predicting prognosis for patients with RCC. In the current survey, adding CRP data to UISS was found, in a Cox regression analysis to improve prognostic accuracy by 2.5% at 2 years (85.3%-87.8%, P <.001) and 3.8% at 5 years (from 80.2%-84.0%, P <.001).

COMMENTARY

CRP is an acute phase protein produced in the liver in response to proinflammatory cytokines. One particularly relevant cytokine in the setting of renal cell carcinoma is IL-6 because renal carcinoma cells have been shown to harbor IL-6 receptors,[4] and to proliferate in vitro when exposed to IL-6.[4,5] Furthermore, serum IL-6 levels, like CRP, have been shown to correlate with RCC survival.[6] In fact, renal carcinoma cells have been shown to secrete IL-6 producing an autocrine growth effect in vitro[7]; a feature that has been speculated to be important in the progression of disease, at least in some patients with this disease.[8]

Thus, it comes as no surprise that CRP is of prognostic importance in RCC. The clinical utility of this observation remains to be determined. It is notable that currently two agents (sorafenib and sunitinib) are being tested in three different clinical trials for post nephrectomy, adjuvant treatment of RCC. It may ultimately prove that pretreatment CRP levels will prove a useful indicator of those who are likely to benefit from such treatment. Furthermore, the value of serial CRP measures to assess early recurrence would seem a worthwhile investigation. ■

Clinical Oncology Alert, ISSN 0886-7186, is published monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
MARKETING MANAGER: Shawn DeMario
MANAGING EDITOR: Iris Young

GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Clinical Oncology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $40.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Customer Service: 1-800-688-2421
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Subscription Prices
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1 year with free AMA Category 1 credits: $289
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(Student/Resident rate: $120).
Multiple Copies
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1-9 additional copies: $215 each; 10 or more copies: $191 each.
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CHOP-Campath for PTCL

ABSTRACT & COMMENTARY

By Andrew Artz, MD, MS

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

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

Synopsis: This multicenter trial evaluated the efficacy of combining alemtuzumab (Campath 1-H) to standard CHOP for peripheral T-cell lymphomas. Among 24 evaluable patients, the complete response rate was 17/24 (71%) using 8 cycles of CHOP plus 30 mg of Campath monthly. Infectious complications were not infrequent and included Jacob-Creutzfeld (JC) virus encephalitis, invasive aspergillosis, CMV reactivation, and bacterial sepsis. CHOP plus Campath has promising disease activity in PTCL although may also lead to increased infectious complications.

Source: Gallamini A, et al. Alemtuzumab (Campath-1H) and CHOP chemotherapy as a first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. *Blood.* 2007;110:2316-2323.

The peripheral T-cell lymphomas (PTCL) are a heterogeneous group of lymphomas that account for <15% of non-Hodgkin's lymphoma diagnoses. Peripheral T-cell lymphoma, unspecified (PTCL-U) is the most common type. Other subtypes include anaplastic large cell (ALCL), angioimmunoblastic-like T-cell lymphoma (AILD-T), extranodal NK/T-cell lymphoma-nasal type, subcutaneous panniculitis-like T-cell lymphoma, enteropathy-associated T-cell lymphoma (EATCL), and hepatosplenic gamma/delta T-cell lymphoma.

Peripheral T-cell lymphomas have a poor prognosis with median survival of < 2 years.[1] Initial treatment frequently consists of standard combination chemotherapy using cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). The prognosis remains < 50% at 5

years, even for treated patients, except for those harboring low-risk features.[2] Thus, novel approaches are warranted to improve outcome for PTCL. The expression of CD52 in PTCL, although variable, raises the possibility of using Campath-1H (alemtuzumab), an anti-CD52 humanized monoclonal antibody.[3]

From June 2003 to December of 2005, 14 Italian institutions within the GITIL (*Gruppo Italiano Terapie Innovative nei Linfomi*) prospectively enrolled 25 patients on this protocol. Treatment consisted of 8 cycles of monthly CHOP chemotherapy and concomitant Campath (CHOP-C). The first four patients received Campath during the first four cycles of CHOP (CHOP-C). Then CHOP without Campath was given in cycles 5-8. Following that, subsequent patients received CHOP-C for all 8 cycles. Campath was administered subcutaneously using standard pre-medication. Escalation during the first course followed a schedule of a starting dose of 3 mg on day -2, 10 mg on day -1, and 30 mg on day 0. For subsequent cycles, 30 mg of Campath was given the day before CHOP. Infection prophylaxis included 400 mg of acyclovir twice a day, sulfamethoxazole/trimethoprim twice a day on alternative days, itraconazole 400 mg/day and ciprofloxacin when the absolute neutrophil count fell below < 500/uL. The Eastern Cooperative Oncology Group NHL response criteria defined responses.

The mean age was 52 years. Central review confirmed PTCL in all but one case, leaving 24 evaluable subjects. The histologic subtypes enrolled included PTCL-U (58%), AILD-T (25%), and alk negative ALCL (12.5%), and EATCL (4%). One third of patients had an international prognostic index (IPI) of 0-1. The remainder had a score of 2-5. In the 15 patients where immunostains were evaluable, 11 showed CD52 positivity and 4 did not (threshold not provided).

The complete and overall response rate was 17/24 (71%) and 18/24 (75%), respectively, as only one patient achieved a PR. Actuarial overall survival was 70% at 1 year and 53% at 2 years whereas progression-free survival was 54% at 1 year and 48% at 2 years. Neutropenia accounted for most of the hematologic toxicity at 34% of chemotherapy cycles. Cytomegalovirus reactivation occurred in 9% of chemotherapy courses. Other infectious complications include one case of J-C virus encephalitis leading to dementia and 2 cases of invasive aspergillosis. One patient developed Pneumocistis carinii pneumonia. One patient was suspected of having atypical mycobacteriosis.

COMMENTARY

Peripheral T-cell lymphomas represent a heterogeneous group of lymphoma subtypes. Results with standard chemotherapy such as CHOP have been disappointing. The improvement in outcomes for B-cell lymphoma, spurred by the use of anti-CD20 antibodies such as rituximab, stands in contrast to the limited progress for T-cell lymphoma. Progress has been severely hampered as an uncommon lymphoma making enrollment on clinical trials difficult.

The majority of PTCL appear to express CD52, making Campath, an anti-CD52 humanized antibody, a reasonable therapeutic consideration. The 71% complete response rate in 24 patients using CHOP plus Campath (CHOP-C) appears to be an incremental gain compared to the historical results of 50% or less using standard CHOP. The authors deserve credit for prospective accrual for this uncommon and highly variable lymphoma. The survival results are sobering: overall survival was approximately 50% at 2 years. The small sample prevents further stratifying by pre-treatment characteristics. Longer time follow-up will be also been needed. Since 1/3rd of patients had low-risk disease by the international prognostic index, it is not possible to conclude that CHOP-C improved outcome. Another recent study of 20 PTCL patients using a 3 week scheduled of CHOP-C showed a similar 65% CR rate.[4] The study closed early due to excessive infectious complications.

Not surprisingly, there were a considerable number of opportunistic and bacterial infections despite a relatively low dose of Campath (30 mg once a month) and close infectious monitoring and prophylaxis. While an appealing strategy would be dose escalation of Campath or shortening CHOP-C cycles (eg every 14 or 21 days), infectious complications might be dose limiting. Another strategy may be employing Campath only in cases where lymphoma cells strongly express CD52.

The results should be taken in the context of other therapeutic options. Autologous transplant in first complete remission has not been successful. Allogeneic transplant, particularly using reduced intensity conditioning, continues to be explored. Randomized studies may be required to determine whether CHOP-C offers a benefit compared to standard therapy.

CHOP-C represents one option for upfront treatment of PTCL but requires aggressive monitoring for infectious complications. ■

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Low Dose Oral Chemotherapy for Indolent NHL in Elderly Patients

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Oral fludarabine and cyclophosphamide were used in combination for initial treatment of non-Hodgkin lymphoma in 25 elderly patients. During an observation period of just over 3 years, 84% were responsive to treatment and there was an overall survival rate of 70%. Hematological and non-hematological toxicity were generally mild and manageable.*

Source: Fabbri A, et al. *Br J Haematol.* 2007;139:90-93.

Fludarabine (Flu) and cyclophosphamide (Cy) are each active in the treatment of indolent lymphoma, and when administered together have a demonstrable synergistic effect.[1] For example, in vitro studies demonstrated that Flu inhibits DNA repair of interstrand cross-links induced after exposure of neoplastic B-lymphocytes to activated Cy. In turn, the incorporation of the F-ara-A (the nucleoside derived from Flu) into lymphocyte DNA was markedly increased by Cy.[2] Thus, Flu-Cy combinations have been tested extensively with excellent anti-neoplastic effects, but at considerable risk for myelosuppression and infectious complications.[3] Attempts at reduction of toxicity have included lower dose regimens, some of which have demonstrated a retention of excellent response rates.[4]

Another feature of this combination is that both drugs have been formulated for oral administration. This convenience, in combination with a reduced dosing strategy was the basis of the current phase II clinical trial in elderly patients with indolent non-Hodgkin lymphoma (NHL). The study, conducted by Fabbri and colleagues at the University of Siena and the University of Genova included 25 elderly (median age 74 years, range 66-85 years) patients with previously untreated NHL. Both Flu (25 mg/m2) and Cy (150 mg/m2) were administered orally for four days, repeated every 28 days for a total of four cycles. Twenty-one (84%) responded favorably to treatment; 10 achieved a complete remission, and 11 met criteria for partial remission. During an observation period of 37 months, there was an overall survival rate of 70% and a median event-free survival of 20 months. Eighteen patients received the entire planned treatment and there were no delays or dose reductions required. In total, only four patients were considered non-responders; two of these had stable disease and two had evidence for disease progression. Thirteen of 21 responding patients had maintained their response after a median observation period of 19 months and the median overall survival (OS) had not been reached at 37 months. As noted, median event free survival was 20 months.

Myelosuppression was the main side effect, although grade 3-4 hematological toxicity was documented in only seven cases (28%) and these patients were treated successfully with growth factor (G-CSF and/or erythropoietin). Infectious complications occurred in five patients. Extrahematological toxicity was mild, consisting of grade 1-2 nausea/vomiting in 24% and one patient who experienced grade 3 peripheral neuropathy.

COMMENTARY

Like most cancer, NHL is a disease of the elderly. While moderately aggressive regimens, such as R-CHOP have proven safe and effective,[5] for those with indolent disease, such may be more than required to maintain excellent disease control. Furthermore, the convenience of oral therapy with the associated reduced need for clinic visits may be particularly advantageous for patients in this age group. However, as with oral therapy in general, this advantage must be balanced by the concern regarding compliance to dose and schedule.[6]

Recently, rituximab has been shown to be highly effective and well tolerated in the treatment of NHL. It is likely that the addition of rituximab to this regimen would favorably increase results including event free and overall survival. However, this may come at an increased risk for infection, a concern that warrants further investigation before widespread application in the community setting.

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Venous Thromboembolism and Prognosis in Pancreatic Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a careful analysis of 227 patients with unresectable or metastatic pancreatic carcinoma treated on protocol with chemotherapy, the development of venous thromboembolism (VTE) was associated with shorter progression-free and overall survival.*

Source: Mandala M, et al. Venous thromboembolism predicts poor prognosis in irresectable pancreatic cancer patients. *Ann Oncology.* 2007;18:1660-1665.

Whereas the occurrence of venous thromboembolism (VTE) is an acknowledged common development in patients with gastrointestinal malignancy, the relationship between the cancer itself, chemotherapy and thrombus formation has not been well established. The aim of the study by Mandala and colleagues was to determine the significance of VTE occurrence in patients with locally advanced (unresectable) or metastatic pancreatic carcinoma. For this, over an approximate 3 year period, 227 patients with Eastern Cooperative Oncology Group performance status (ECOG-PS) < 2 and nonresectable pancreatic cancer were identified from local registries and clinical trials. Of these 28 (12.3%) had VTE at the time of diagnosis, 15 (6.6%) developed VTE during chemotherapy and an additional 16 (7%) had VTE both prior to and during chemotherapy. All patients had received chemotherapy; 35% with PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine), and 65% with either gemcitabine alone or in combination with cisplatin. Of the total group, 1 patient had a complete response, 54 (24.8%) achieved partial response, 73 (33.5%) had stable disease and 90 (41.3%) had progressive disease. Analysis by univariate and multivariate logistic models examining the prognostic effect of synchronous VTE, the occurrence of VTE during chemotherapy, and the presence of VTE irrespective of the time of occurrence revealed that two factors seemed to be independently predictive of progressive disease; the use of chemotherapy other than PEFG (odds ration [OR] 6.38, 95% confidence interval [CI] 3.12-13.03, $P = 0.0001$) and synchronous VTE (ie, VTE that occurred prior to treatment; OR 2.90, 95% CI 1.40-6.84, $P = 0.005$). No statistically significant effect of occurrence of VTE during chemotherapy on response to treatment was observed. Over the three years, all but 5% of the patients had died. The median progression free survival (PFS) and overall survival (OS) were 5 and 9.6 months, respectively. With regard to PFS, by multivariate analysis, stage IV disease, and VTE occurring before or during chemotherapy were significant negative risk factors. Curiously, for each 5 year age increase, there was a lower risk of progression (hazard ratio [HR] 0.92, 95% CI 0.86-0.99, $P = 0.044$). Regarding overall survival, stage IV disease and VTE occurring before or during chemotherapy were significant by univariate analysis but only stage IV disease and VTE occurring during chemotherapy were statistically significant.

COMMENTARY

Thus, in an analysis of a homogeneous cohort of advanced pancreatic caner patients there is now irrefutable evidence that VTE, whether present before, or developed during treatment, is a negative prognostic factor. Certainly, the concept is not new[1, 2] but the current report offers an evaluation in the context of time of occurrence (prior to, or during chemotherapy), tumor stage and chemotherapy response. The analysis, which relied on a retrospective review for the presence of VTE, the actual number is likely to be an underestimate. Furthermore, all patients had been treated with chemotherapy and were ECOG PS ≤ 2, and perhaps those with a greater number of comorbid conditions or functional impairments that would preclude clinical trial would have an even higher rate of VTE.

Given that VTE occur with increased frequency and indicate a more negative outcome in patients with locally advanced or metastatic pancreatic cancer, would there be any value in primary prophylaxis? Unfortunately, oral anticoagulation with vitamin K antagonists is problematic due to drug interactions, malnutrition and liver dysfunction. Furthermore, both recurrent VTE and hemorrhage are more common in cancer patients when treated with vitamin K inhibitors such as Coumadin. However, treatment with low molecular weight heparin (LMWH) has proven to be effective and relatively safe in this setting.[3] Such might reduce the rate of new or recurrent VTE but its effect on tumor growth, spread and chemotherapy response remains to be fully clarified.

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Examining The Range of Therapy for Elderly Patients with Hematological Malignancy

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: The management of acute myelogenous leukemia in elderly patients has been challenging and there has developed a pervasive pessimism about the role of chemotherapy in management. Two recent reports may counter this with demonstration of a benefit for induction chemotherapy and, in selected cases, both efficacy and safety of stem cell transplantation using nonmyeloablative conditioning.

Sources: Baz R, et al. *Cancer.* 2007;110:1752-1759; Falda M, et al, for the Gruppo Italiano Trapianto Midollo Osseo (GITMO). *Am J Hematology.* 2007; 82:863-866.

Malignant disease occurring in older people is not, in general, more resistant to treatment but the presence of comorbidities and functional impairments may preclude the application of effective treatment.[1] A notable exception to this is acute myelogenous leukemia, the successful treatment of which is markedly reduced in the elderly, even when standard chemotherapy is administered.[2] This may be because the disease is quite different in older patients with more frequent antecedent myelodysplasia and acquired genetic mutations rendering cells resistant to treatment.[3] In a wide range of clinical protocols employing chemotherapy combinations of varying intensity a common thread has been a low response rate and high treatment related mortality.[4,5] In fact, some have questioned the value of chemotherapy in this setting compared with supportive care alone.[6] In one study conducted nearly two decades ago newly diagnosed patients over the age of 65 were treated with daunorubicin, vincristine and cytarabine or supportive care alone and the modest benefit for treated patients in terms of overall survival (10 weeks) was almost entirely spent in the hospital.[7] In a separate trial, Tilly and colleagues compared less intense chemotherapy (low-dose cytarabine) vs standard induction chemotherapy (daunorubicin and cytarabine) only to find no statistically significant survival difference between the 2 groups (median survival 8.8 months in the nonintensive chemotherapy group vs 12.8 months in the induction chemotherapy group). As with the prior study, those receiving the more intensive therapy had more time in the hospital and also required more transfusions and sustained greater treatment-related mortality.[8]

Although there has not been a significant change in standard chemotherapy approaches to AML over the past two decades, there have been significant advances in supportive care. Furthermore, with the rapidly aging population the issue of optimal approach to aggressive hematological malignancy has resurfaced as a critical domain for clinical research. Accordingly, two recent publications are of interest.

Baz and colleagues from the Cleveland Clinic performed a retrospective review of AML patients 60 years and older evaluated and/or treated at their Center. Forty-four patients who, for one reason or another, did not receive induction chemotherapy were matched as best possible (by propensity analysis) to 138 patients who received an anthracycline-based regimen. The unadjusted median survival of patients who did not receive induction chemotherapy was 53 days, compared with 197 days ($P < 0.001$) for those who did. Upon adjusting for age, gender, race, leukocyte count at presentation, cytogenetic changes, history of prior hematological disorder, and comorbidities, not receiving induction chemotherapy was still associated with worse survival (hazard ratio [HR] of 1.88; 95% confidence interval [CI] 1.15-3.05, $P = 0.01$). The authors conclude that for older adults with AML, treatment with induction chemotherapy is associated with improved outcomes.

The second report was that of an Italian multicenter group (Gruppo Italiano Trapianto Midollo Osseo, GITMO) who treated a total of 32 patients over the age of 60 years (median age 62 years, range 60-70) with hematological malignancy with nonmyeloablative allogeneic stem cell transplantation. The great majority of these patients had either AML or myelodysplastic syndrome. Treatment consisted of fludarabine (30mg/m2 x 3-5 days) and 200 cCy total body irradiation (TBI) followed by hematopoietic stem cell transplantation (HSCT) from a matched-sibling donor. Neutrophil recovery occurred in all patients at a median time of 16 days (range 9-34 days) and by day 30, 10 patients had > 95% donor chimerism and 19 patients had mixed chimerism.

Transplant-related mortality at 100 days and at 1 year was 6% and 10% respectively. The probabilities of 2-year overall survival (OS) and progression-free survival (PFS) for patients with early disease were 77% and 64% respectively. However, for those who were transplanted with advanced stage disease, none were alive at 2 years.

COMMENTARY

The data from these two articles are far from conclusive with regard to management of elderly patients with AML or other advanced hematological malignancy. Nonetheless, they support an evolving intensified effort to define optimal management for those patients in this age group. Notable in this regard is that those patients who received treatment (median age 68 years in the Cleveland Clinic study and 62 years in the Italian study) might not reflect the typical leukemic patient in the community, who is likely to be older and have more comorbidities than those included herein.

Yet, it appears that older patients (Cleveland Clinic study) benefit from induction therapy and that selected patients in the 60-70 year age group without a large tumor burden from nonmyeloablative HSCT (GITMO). These findings would have been unlikely two decades ago and probably speak to the advances in supportive care, including better antibiotics, the use of growth factors, attention to nutrition and, for the case of HSCT lower dose preparative regimens and better prevention and treatment of graft vs host disease.

The bottom line is that we still have a lot to learn about the management of leukemia in the elderly. Nonetheless, these reports are encouraging, and provide rationale for continued investigation to define optimal treatment strategies. Furthermore, we now have ammunition (albeit limited) to combat the pervasive therapeutic nihilism that had settled in on the basis of those investigations of two decades ago.

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1. Publication Title	2. Publication No.	3. Filing Date
Clinical Oncology Alert	0 8 8 6 - 7 1 8 6	10/1/07
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Person: Robin Salet; Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*: Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*: Iris Young, same as above

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13. Publication Name: Clinical Oncology Alert — 14. Issue Date for Circulation Data Below: September 2007

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CME Questions

46. Which of the following factors is not of prognostic value in patients with renal cell carcinoma?
a. age
b. stage
c. gender
d. CRP
e. ECOG performance status

47. What were the results of CHOP plus alemtuzumab (Campath) chemotherapy in patients with peripheral T-cell lymphomas?
a. A 71% complete response rate in 24 patients.
b. No infectious complications.
c. Synergy with rituximab.
d. A clear survival benefit over CHOP.

48. An oral regimen of fludarabine and cyclophosphamide for the treatment of indolent NHL in elderly patients was shown by Fabbri and colleagues to be associated with:
a. an excellent response rate but unacceptable hematological toxicity.
b. an excellent response rate and mild to moderate hematological toxicity.
c. negligible toxicity but unacceptable efficacy when compared to parenteral chemotherapy.
d. an excellent response rate but unacceptable extrahematological toxicity (particularly, nausea and vomiting).

49. With regard to progression-free survival, which of the following factors is NOT associated with a poorer prognosis in patients with locally advanced or metastatic pancreatic cancer, according to the data presented by Mandala, et al?
a. advancing age
b. VTE occurring prior to chemotherapy
c. VTE occurring during chemotherapy
d. stage IV disease

Answers: 46 (c); 47 (a); 48 (b); 49 (a)

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- to present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- to describe new advances in the field of oncology.

In Future Issues: **Multiple Benign Breast Lesions: A Risk for Progression to Cancer?**

PHARMACOLOGY WATCH

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Are Thiazolidinediones (TZDs) Safe?

In this issue: *Are thiazolidinediones safe? New study shows Zometa reduces risk of hip fractures and improves survival; Merck HIV vaccine proven ineffective in clinical trials; no causal association found between exposure to mercury from thimerosal; and FDA approvals.*

There's no hotter topic in medicine right now than the safety of the thiazolidinediones (TZDs) rosiglitazone (Avandia) and pioglitazone (Actos). Several meta-analysis have pooled data from multiple clinical trials and come to different conclusions regarding the safety of the drugs. The September 12 issue of *JAMA* contained two papers, both meta-analysis, the of first which suggests that pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. An increase in heart failure was noted, although no increase in mortality (*JAMA* 2007; 298:1180-1188).

The second paper looked at rosiglitazone and noted that in patients with impaired glucose tolerance or type 2 diabetes, use of rosiglitazone for at least 12 months was associated with a significantly increased risk of myocardial infarction and heart failure, again without a significant increase risk of cardiovascular mortality (*JAMA* 2007; 298:1189-1195). This followed on conflicting meta-analysis regarding the risk of rosiglitazone published in the *New England Journal of Medicine* in June and July, the first of which suggested the rosiglitazone was associated with an increase risk of myocardial infarction and increased risk of death from cardiovascular causes (*NEJM* 2007; 356:2457-2471), while the second showed an increased risk of heart failure but no increased risk of myocardial infarction or death from cardiovascular causes (*NEJM* 2007;357:28-38). The studies led to congressional hearings, multiple editorials in medical journals and eventually led the FDA to recommend black box warnings regarding the risk of heart failure for both drugs in July. But despite cries from consumer groups suggesting that this was the Cox-2 debacle redux, the FDA stopped short of taking rosiglitazone off the market. The most recent entry into the fray is a new meta-analysis from the Lahey Clinic in Boston. This review analyzed over 3000 studies of which 7 were used for the analysis—all randomized double-blind clinical trials of drug-related congestive heart failure in prediabetic or diabetic patients given either rosiglitazone or pioglitazone. In over 20,000 patients, 360 had congestive heart failure, 214 on TZDs and 146 on comparators. As with other studies there was an increase risk of heart failure associated with both drugs (relative risk 1.72, 95% CI 1.21-2.24, P= 0.002), but again no increase in cardiovascular death was noted with either drug (RR 0.93). The authors suggest that TZDs cause worsening heart failure, but are not associated with progressive systolic or diastolic dysfunction of the left ventricle that leads to death. They also suggest that more studies are needed (*Lancet* 2007;370:1129-1136). The take home message from all the studies is to use caution in TZDs in patients with diabetes and heart failure (NYHA I and II), and to carefully monitor patients for worsening signs and symptoms including weight gain and edema. Initiation of these drugs in patients with established NYHA Class III or IV heart failure is contraindicated.

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) 262-5413. E-mail: iris.young@ahcmedia.com.

Zometa and hip fractures

A single 5 mg infusion of zoledronic acid (Zometa) within 90 days of a hip fracture reduced the risk of new fractures and improved survival according to new study. Zoledronic acid is a long acting bisphosphonate that is approved for once yearly treatment of postmenopausal osteoporosis. The drug is effective at reducing vertebral, hip, and non-vertebral fractures in women with osteoporosis. In this current study, 1065 men and women with hip fractures were assigned to receive yearly intravenous zoledronic acid 5 mg IV or placebo, the infusions were administered within 90 days of surgical repair of a hip fracture. All patients received vitamin D and calcium. Mean age was 74.5 years, with approximately 75% women. The rate of new clinical fracture was 8.6% in the zoledronic acid group and 13.9% in the placebo group (35% risk reduction, $P = 0.001$). The respective rates of new clinical vertebral fractures were 1.7% vs 3.8% ($P = 0.02$) and for non-vertebral fractures 7.6% vs 10.7% ($P = 0.03$). The death rate was 28% less in the zoledronic acid group (101 of 1054 [9.6%] vs 141 of 1057 [13.3%], $P= 0.01$). No cases of osteonecrosis of the jaw were reported and no adverse effects of healing fractures were noted. The authors conclude that an annual infusion of zoledronic acid within 90 days of a low trauma hip fracture was associated with reduced rate of new fractures and improved survival (published early at www.NEJM.org September 17, 2007).

Merck HIV Vaccine Ineffective in Clinical Trial

After years of development and clinical trials Merck has announced that their HIV vaccine is ineffective in a large clinical trial, and the company has halted further test vaccinations. Other HIV vaccines have also failed but many had hoped that the Merck vaccine, which worked by stimulating T cells, might be more effective. The trial, which was begun in 2004 vaccinated 3000 uninfected volunteers in the US and Latin America. Among 741 patients who received a least one dose of the vaccine, 24 new HIV infections were identified, compared to 21 infections in 762 patients who received placebo. Work continues on other HIV vaccines, currently 30 worldwide are in clinical trials, but the failure of the Merck vaccine is seen is a major setback for HIV researchers.

Thimerosal and Mercury Exposure

Thimerosal has been the subject of intense scrutiny for years regarding its potential link to various neuropsychological deficits in children. Thimerosal has been used as a preservative in vaccines and gamma globulin for decades, although it is rarely used now because it is metabolized to mercury and thiosalicylate, potentially leading to high mercury levels in children. In a new study from the CDC and several large HMOs, 1047 children between ages of seven and 10 years were enrolled and tested for 42 neuropsychological outcomes, then the medical records were examined for history of exposure to mercury from thimerosal. Prenatal mercury exposure from thimerosal was associated with better performance on one measure of language and poor performance on one measure of attention and executive functioning. Exposure in infancy up to seven months old was associated with better performance in one measure, fine motor coordination, and on one measure of attention and executive functioning. Increasing mercury exposure from birth to 28 days was associated with poorer performance on one measure of speech articulation and better performance on one measure of fine motor coordination. The authors conclude that they could not find a causal association between early exposure to mercury from thimerosal and deficits in neuropsychological functioning at age 7 to 10 years (*NEJM* 2007; 357: 1281-1292).

FDA Actions

Eli Lilly has received approval from the FDA to market raloxifene (Evista) for the indication of reducing the risk of breast cancer in postmenopausal women with osteoporosis and postmenopausal women who are at high risk for invasive breast cancer. Raloxifene is a selective estrogen receptor modulator (SERM) that is already approved for prevention and treatment of osteoporosis in postmenopausal women. The drug was recently required to add labeling regarding an increased risk of fatal strokes in women taking the drug. It also carries a black box warning regarding risk of thromboembolism in women who are at high risk (those with an active or past history or thromboembolism).

Just in time for the winter flu season, the FDA has approved nasal influenza vaccine (FluMist) for use in children between the ages of 2 and 5. Previously the vaccine was only approved for children 5 years old and older and adults up to age 49. The CDC is recommending all children between the ages of 6 months to 59 months receive a flu vaccine. Children ages 2-8 who have never received a flu vaccine will initially require two doses of fluMist at least one month apart.

The FDA has approved a new oral granules form of terbinafine for the treatment of tinea capitis (ringworm) in children. The preparation may be sprinkled on food, allowing easier administration to children who may not otherwise take medicine over the two weeks required to treat tinea. Terbinafine granules are indicated for the treatment of tinea capitis in children age 4 years and older. It is marketed by Novartis AG as Lamisil Oral Granules. ■