Providing Evidence-based Clinical Information for 24 Years

CLINICAL ONCOLOGY ALERT

A monthly update of developments in cancer treatment and research

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

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.

Lenalidomide Active for Non 5q-Low Risk MDS

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: *Lenalidomide is highly effective for low risk MDS associated with a deletion(5q). Raza and colleagues report on lenalidomide for low to intermediate-1 (int-1) risk MDS who were transfusion dependent but without a deletion(5q). Patients received 10 mg daily of lenalidomide either continuously or 21 out of 28 days. Grade 3 and 4 neutropenia and thrombocytopenia occurred in 25 and 20% respectively. Among the 214 patients, 43% responded of which 26% became transfusion independent and the hemoglobin exceeded 10 g/dL. Lenalidomide is an option for red blood cell transfusion dependent low risk MDS, even in patients without a 5q-deletion.*

Source: Raza A, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other then deletion 5q. *Blood.* 2008;111:86-93.

MYELODYSPLASTIC SYNDROMES (MDS) COMPRISE A HETEROgeneous group of disorders characterized by peripheral blood cytopenias, bone marrow hyperplasia, and a proclivity toward progression to acute myeloid leukemia. Prognostic scoring systems such as the International Prognostic Scoring System (IPSS) stratify prognosis and thus guide therapy.[1] For those harboring high-risk IPSS scores, usually due to the presence of increased marrow myeloblasts and/or an adverse karyotype, a short progression to AML and death leads treatment to focus on disease reduction. Lower-risk MDS often manifests a smoldering course where anemia dominates the clinical picture. Anemia can lead to severe fatigue, red blood cell transfusion dependence, and transfusional iron overload. Lenalidomide is an oral thalidomide analog that has marked activity and FDA approval for low-risk MDS harboring a chromosome 5q interstitial deletion.[2]

VOLUME 24 • NUMBER 2 • FEBRUARY 2008 • PAGES 9-16

NOW AVAILABLE ONLINE
www.ahcmedia.com

In this trial, Raza and investigators report on lenalidomide for low-risk MDS without the 5q-syndrome. Patients had MDS with an IPSS of low or int-1-risk and required 2 units or more of red blood cells within the prior 8 weeks. Patients with baseline neutropenia (< 500/uL) or thrombocytopenia (<50,000/uL) were excluded because of the known cytopenias related to lenalidomide.

Among the 214 patients enrolled, the median age was 72 years and 65% required 2 or more red blood cell units per month at baseline. The majority had WHO subtypes of refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS). One hundred patients were treated at 10 mg daily of lenalidomide orally days 1-21 on a 28-day schedule. After protocol modification, 114 subsequent patients received lenalidomide 10 mg daily continuously.

Grade 3 or 4 neutropenia occurred in 25% and thrombocytopenia in 20%. Rash and pruritus were seen in 24 and 21%, respectively, although rarely reaching grade 3. Using the modified IWG 2000 response criteria, 43% responded to treatment with 26% of all patients treated achieving red blood cell transfusion independence (TI) and a hemoglobin > 10.0 g/dL. Among those achieving red blood cell transfusion independence (TI), the median time to TI was 4.8 weeks, 90% achieved this milestone by 16.9 weeks, the median duration of TI was 40 weeks, and in 36% (n = 20) TI lasted for greater then 1 year. Greater red blood cell dependence at baseline reduced the probability of responding. Only 47 patients had a clonal cytogenetic abnormality, of whom 4 had a complete cytogenetic response and 5 had a partial cytogenetic response. During treatment, only 2 of 27 patients with > 5% blasts had a 50% or greater reduction in marrow blasts.

COMMENTARY

In this study, Raza and colleagues report reasonable activity of lenalidomide, as measured by a reduction in red blood cell transfusion dependence, in low-risk transfusion dependent MDS patients without the 5q- cytogenetic abnormality. Among the 214 patients enrolled, 43% met objective response criteria and 26% became transfusion independent (TI) and had hemoglobin > 10 g/dL. The median time to TI was only about 5 weeks. Most (90%) who achieved TI had done so by just over 4 months. Thus, one may need to wait 4 months before determining if lenalidomide is effective for a patient. The two dosing strategies of 10 mg per day for 21 of 28 days and continuous daily dosing had similar efficacy.

Toxicities were as expected with grade 3 or 4 neutropenia and thrombocytopenia occurring in 25% and 20% respectively. Patients could not have severe neutropenia or thrombocytopenia at baseline. Using lenalidomide in MDS patients will necessitate close monitoring for cytopenias, especially if used in those with baseline neutropenia or thrombocytopenia.

The results mirror the results the data reported in the initial studies of lenalidomide for MDS.

The results are interesting. On one hand, they are clearly less impressive than the activity in 5q- MDS with a 36% complete cytogenetic response rate and 67% achieving TI[2,3] compared to a 9% cytogenetic response rate and 26% achieving TI in this study. Nevertheless, 5q- patients represent only a small subset of MDS patients and these results apply to a larger cohort.

Now the ultimate question arises how to sequence lenalidomide in MDS treatment as the therapeutic arsenal for MDS has grown to include ESA's, immunosuppression (particularly for HLA-DR 15 positivity), and hypomethylating agents (5-azacytadine and decitabine). One should always begin the process of hematopoietic cell transplant for the select patients who might be eligible. Lenalidomide obviously will continue to be the choice for deletion (5q) low-risk MDS. For patients with low risk MDS and a hemoglobin < 10 g/dL, a low transfusion burden, and a relatively low serum EPO level (ie, < 200 mU/mL or < 500 mU/mL), ESA therapy +/- G-CSF remains a reasonable therapy.[4] Lenalidomide can now be considered an option for patients who are unlikely to respond or where ESA therapy has failed. Diligent monitoring for

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 PRODUCT 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.
This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information
Customer Service: 1-800-688-2421
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: iris.young@ahcmedia.com

Subscription Prices
United States
1 year with free AMA Category 1 credits: $289
Add $17.95 for shipping & handling.
(Student/Resident rate: $120).
Multiple Copies
Discounts are available for group subscriptions. For pricing information, call Tria Kreutzer at (404) 262-5482.
1-9 additional copies: $215 each; 10 or more copies: $191 each.
Canada
Add GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation
AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
AHC Media LLC designates this educational activity for a maximum of 25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.
This CME activity is intended for the oncologist. It is in effect for 36 months from the date of the publication.

AHC Media LLC

Questions & Comments
Please call Iris Young, Managing Editor, at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

cytopenias is required. Controlled studies are needed comparing hypothemethylating agents and lenalidomide for transfusion dependent low-risk MDS. ■

References

1. Greenberg P, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood.* 1997;89:2079-2088. Erratum in *Blood* 1998 Feb 1;91(3):1100.
2. List A, et al. Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med.* 2005;352:549-557.
3. List A, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med.* 2006;355:1456-1465.
4. Hellstrom-Lindberg E, et al. *Br J Haematol.* 2003;120:1037-1046.

Bevcizumab Plus Interferon Alfa 2a for Metastatic Renal Carcinoma

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a European multicenter trial of interferon alfa with or without bevacizumab for treatment of metastatic renal carcinoma, response rate and progression free survival was superior for those receiving the combination. Future trials, particularly those intending to measure long-term survival will need to also include the newly available tyrosine kinase inhibitors.*

Source: Escudier B, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomized, double blind phase III trial. *Lancet.* 2007;370:2103-2111.

Renal cell carcinoma is refractory to standard chemotherapeutic approaches and survival for those with metastatic disease is limited.[1,2] Approximately one-third of patients present with metastatic disease and almost another third will relapse with metastatic disease after initial curative-intent nephrectomy.[3]

Until recently, the standard systemic therapy has been with either interferon or interleukin-2. However, response rates had remained disappointing (around 20%) and there was substantial toxicity. Interferon was shown to modestly enhance median overall survival to 13 months[4] and high dose interleukin-2 resulted in apparently curative outcomes in a small percentage (5-10%).[5]

A typically vascular tumor, renal carcinoma has been associated with mutations of the von Hippel-Lindau tumor suppressor gene and associated over expression of vascular endothelial growth factor (VEGF).[6] Currently, various strategies are being explored to inhibit angiogenesis, and one involves treatment with the humanized anti-VEGF monoclonal antibody bevacizumab. In phase II studies in previously untreated patients with metastatic renal cell carcinoma, bevacizumab monotherapy resulted in a median progression-free survival of 8.5 months[7] and some had durable responses lasting as long as 3-5 years.[8]

Escudier and colleagues report the findings from a European multicenter, double blind, phase III trial in which 649 patients with previously untreated metastatic renal cell carcinoma received interferon alfa-2a (9 MIU subcutaneously three times weekly) and either bevacizumab (10 mg/kg) or placebo every two weeks.

At the time of unblinding, 230 progression events and 114 deaths had occurred among the 325 patients who had been randomized to the bevacizumab/interferon alfa arm compared with 275 events and 137 deaths among the 316 in the placebo/interferon arm.

Median duration of progression-free survival was significantly longer in the bevacizumab/interferon alfa group than it was in the control group (10.2 months vs 5.4 months; hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.52-0.75; $p = 0.0001$). Improved progression-free survival was observed with bevacizumab/interferon alfa for all risk categories. Deaths due to adverse events occurred in 8 patients (2%) who received one or more doses of bevacizumab and 7 (2%) of those who did not receive the drug. Three deaths among the bevacizumab-treated patients were considered by the investigators to be possibly related to the drug. The most commonly reported grade 3 or worse adverse events were fatigue and asthenia, and these occurred with comparable frequencies in the two arms.

■ COMMENTARY

As originally written, this large multicenter trial was designed to address the effect on overall survival of bevacizumab added to interferon in patients with metastatic renal cancer. However, during the trial promising new therapies were shown to have signifi-

cant activity in this clinical setting and it became apparent that their introduction as second line therapy would likely confound analysis of overall survival. Among these new agents are the tyrosine kinase inhibitors sunitinib[9] and sorefenib.[10] Accordingly, the investigators in consultation with regulatory agencies amended the protocol to define primary results in terms of progression-free survival (PFS) at this time, and report overall survival at a later date.

In this regard, it is also quite apparent that bevacizumab is an active agent against renal cancer; a welcome finding for a disease with a history of failed therapies. Now, however, the addition of the tyrosine kinase inhibitors provides GU oncologists with a whole new set of questions and a calling to provide rational clinical trials to address optimal treatment for a cadre of heretofore unresponsive patients. Topics such as the need for the moderately toxic interferon and the appropriate sequencing or combination of bevacizumab and TK inhibitor will be prime questions to address in well constructed clinical trials. ■

References

1. Motzer RJ, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2004;22(3):454-463.
2. Motzer RJ, et al. Renal-cell carcinoma. *N Engl J Med.* 1996;335(12):865-875.
3. Rouviere O, et al. Nonmetastatic renal-cell carcinoma: is it really possible to define rational guidelines for post-treatment follow-up? *Nat Clin Pract Oncol.* 2006;3(4):200-213.
4. Coppin C, et al. Immunotherapy for advanced renal cell cancer. *Cochrane Database Syst Rev.* 2005(1):CD001425.
5. Parton M, et al. Role of cytokine therapy in 2006 and beyond for metastatic renal cell cancer. *J Clin Oncol.* 2006;24(35):5584-5592.
6. Brieger J, et al. Inverse regulation of vascular endothelial growth factor and VHL tumor suppressor gene in sporadic renal cell carcinomas is correlated with vascular growth: an in vivo study on 29 tumors. *J Mol Med.* 1999;77(6):505-510.
7. Yang JC, et al. *N Engl J Med.* 2003;349(5):427-434.
8. Yang JC. Bevacizumab for patients with metastatic renal cancer: an update. *Clin Cancer Res.* 2004;10(18 Pt 2):6367S-70S.
9. Motzer RJ, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA.* 2006;295(21):2516-2524.
10. Escudier B, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007;356(2):125-134. Erratum in *N Engl J Med.* 2007 12;357(2):203.

Confirming a Role for Adjuvant XRT in the Management of Pancreatic Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Two recent reports examining NCI-SEER registry data demonstrate improved overall survival when external beam radiation therapy is applied in an adjuvant setting for those with pancreatic cancer.*

Sources: Hazard L, et al. Radiation therapy is associated with improved survival in patients with pancreatic adenocarcinoma: results of a study from the Surveillance, Epidemiology, and End Results (SEER) registry data. *Cancer.* 2007;110:2191-2201.

Artinyan A, et al. Improved survival with adjuvant external beam radiation therapy in lymph node-negative pancreatic cancer. A United States Population-based assessment. *Cancer.* 2008;112:34-42.

THE ADJUVANT USE OF EXTERNAL BEAM RADIATION for patients with pancreatic cancer has been controversial.[1] However, two recent reports, both of which capitalized on the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) registry have demonstrated added benefit in selected clinical settings. Hazard and colleagues from the University of Utah performed a retrospective analysis on 3008 patients reported to the registry from 1988 to 2002 who had adenocarcinoma of the pancreas and who underwent cancer-directed surgery. Overall and cancer-specific survival for these patients was performed using the Kaplan-Meier method. Comparative risks of mortality were evaluated by using multivariate adjusted Cox regression models.

Of 3008 patients, 1267 (42%) received radiation therapy. Overall survival improved significantly in patients who received radiation therapy, with a median survival of 17 months and a 5-year overall survival rate of 13% in patients who received radiation compared with 12 months and 9.7%, respectively, for patients who did not receive radiation therapy (P <.0001). On multivariate analysis, radia-

tion therapy was associated with improvement in overall survival in patients who had direct extension beyond the pancreas and/or regional lymph node involvement ($P < .01$) but not in patients with T1-T2N0M0 disease ($P > .05$). Radiation therapy was associated with improvement in cause-specific survival in patients who had regional lymph node involvement ($P < .02$) but not in patients who had T1-2N0M0 disease or direct extension beyond the pancreas without lymph node involvement ($P > .05$). Differences in overall and cause-specific survival among patients who received preoperative vs postoperative radiation therapy did not reach statistical significance.

In a report published in the same journal just a few months later, Artinyan and co-workers from the City of Hope National Medical Center in Duarte, California (and also analyzing SEER registry data), undertook a more focused look at the success of adjuvant radiation therapy for patients over the same time period (1988-2003). Their focus was on localized, node negative pancreatic cancer and not on those with more advanced disease. Once again, Kaplan-Meier survival curves were constructed to compare overall survival between patients who did and did not receive adjuvant radiation therapy (RT). Multivariate Cox regression analysis was also used to determine the prognostic value of RT when additional clinicopathologic factors were assessed. In this analysis, particular attention was paid to the potential treatment selection bias of patients who had survival 3 months or less.

The analysis included data from 1930 surgical patients with N0 disease. For the overall group, the median survival was 17 months. Irradiated patients had significantly better survival compared with non-irradiated patients (20 months vs 15 months, respectively; $P < .001$). On multivariate analysis, having received adjuvant RT, age, grade, tumor classification, and tumor location remained independent predictors of survival. However, when patients with survival < 3 months were excluded from the analysis, the observed benefit of RT (in univariate comparison) was no longer apparent. However, on multivariate analysis, having received RT remained an independent predictor of improved overall survival (HR, 0.87; 95% CI, 0.75-1.00; P=5.044).

COMMENTARY

These two reports, capitalizing on the rich SEER data base, support a role for adjuvant external beam radiation therapy in conjunction with surgery for patients with pancreatic cancer. Long-term survival remains poor, but median survival appears to be enhanced by 4 to 5 months in treated patients. Of course, retrospective analyses such as these run the risk of treatment bias, but both research teams controlled as best possible by rigorous multivariate analysis.

What seems somewhat surprising is that analysis of basically the same dataset led to two different conclusions regarding treatment of node negative, locally confined disease. The Utah report (Hazard, et al) was not able to demonstrate RT-enhanced survival for those with T1-T2N0M0 in contrast to the significant RT survival enhancement for those with locally more advanced disease and/or lymph node involvement. The City of Hope analysis (Artinyan et al), was confined to that group which had shown no RT benefit in the Utah study, ie, locally confined, node negative. In their analysis, however, there was a larger cohort (1930 subjects compared with approximately 400 with that stage in the Utah report). The larger sample size may alone explain the different finding, although perhaps it also relates to the elimination of early death bias in the City of Hope report, an approach not taken by the Utah group.

Despite the minor discrepancy, the data are for the most part consistent and demonstrate a modest improvement in survival in those who had received adjuvant RT in conjunction with surgery. Whether such will become the standard approach will depend on local patterns of care and the experience of radiation oncologists applying external beam therapy under oftentimes difficult circumstances. Furthermore, the survival advantage needs to be presented in the context of added morbidity, an aspect not thoroughly evaluated in these reports. It is clear that adjuvant RT is warranted under certain circumstances, and these circumstances include patient directives as well as the availability of talented radiation oncologists. ■

Reference

1. Bergenfeldt M, Albertsson M. Current state of adjuvant therapy in resected pancreatic adenocarcinoma. *Acta Oncol.* 2006;45(2):124-135.

Statins and Breast Cancer: Yes, No, or Maybe

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Statin drugs have been increasingly used for management of hypercholesterolemia. Preclinical studies indicated an antiproliferative effect* in vitro *and in rodent models of breast cancer. The current report is one of several that indicate a lack of evidence for reduction in breast cancer risk among statin users. However, the overall use of drugs in this class in the study cohort (7%) and the relatively short duration of use (approximately 4 years) suggest that the question is not completely resolved.*

Source: Pocobelli G, et al. *Cancer.* 2008;112:27-33.

In vitro[1] AND ANIMAL STUDIES[2] HAVE DEMONSTRATED an antiproliferative effect of statin drugs (3-hydroxyl-3 methylglutaryl coenzyme A reductase inhibitors) in certain breast cancer tumor models and these have engendered an intense interest to examine whether use of these drugs would be associated with reduced risk for breast cancer. To address this, Pocobelli and colleagues analyzed data from a population-based case-control study in which women 50 years of age or older with invasive breast cancer diagnosed between 1995-2001 were identified from population-based cancer registries in Wisconsin, Massachusetts, and New Hampshire. Controls were randomly selected from lists of licensed drivers and Medicare beneficiaries. Information on the use of statins and other breast cancer risk factors was ascertained from structured telephone interviews.

Overall, 7% of women ever used a statin and the mean cumulative duration of statin use was slightly greater for cases than controls (4.9 years vs 4.5 years, respectively). Analysis based upon the type of statin used, revealed that prior or current use of lipophilic statins as a group (simvastatin, lovastatin, and fluvastatin) and ever use of the hydrophilic statin pravastatin were also not associated with breast cancer risk. However, when examined singly, ever use of fluvastatin was associated with a decreased risk of breast cancer (odds ratio [OR], 0.5; 95% confidence interval, 0.3-0.8) but the reduction in risk was statistically significant only among users of less than 5 years (OR, 0.5; 95% CI, 0.3-0.9).

COMMENTARY

Thus, the use of statins overall was not found to be associated with reduced breast cancer risk and this is consistent with a large literature, including a meta-analysis of 7 randomized trials and 9 observational studies examining breast cancer among statin users.[3] The current multicenter population-based case-control study examined statins as a group, and specific drugs individually. However, the relatively short duration of treatment and low prevalence of statin use (7%) might suggest that, despite the negative result, the final answer might not be in. Also, the underlying condition for which the statin was prescribed (generally, hypercholesterolemia) might itself be a risk factor for breast cancer. An appropriate comparison, as noted by the authors, would be a comparison of statin users with users of other cholesterol-lowering agents over a long period of time. Unfortunately, the numbers were inadequate in the current study to result in reliable conclusions, and are unlikely in the near future outside of a randomized trial, because of the widespread use of drugs in this class at the current time. Alternatively, a placebo-controlled randomized study in women considered at high risk might be instructive. ■

References

1. Muck AO, et al. *Int J Clin Pharmacol Ther.* 2004;42(12):695-700.
2. Campbell MJ, et al. *Cancer Res.* 2006;66(17):8707-8714.
3. Bonovas S, et al. *J Clin Oncol.* 2005;23(34):8606-8612.

Docetaxel for Advanced Prostate Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: A randomized multicenter trial conducted almost a decade ago and reported in 2004 showed docetaxel plus prednisone to be superior to mitoxantrone plus prednisone for patients with hormone refractory prostate cancer. At the time of that report approximately 50% of the cohort had died. The current report examines the survival curves including the additional 310 patients who had died since the initial report. The earlier findings of superior survival for those treated with docetaxel (at 3 week intervals) and prednisone compared to mitoxantrone and prednisone stand up. Thus, this should be the preferred combination for those treated with chemotherapy off study, and the standard to which experimental approaches is be compared.

Source: Berthold DR, et al. *J Clin Oncol.* 2008;26:242-245.

INITIAL THERAPY FOR METASTATIC PROSTATE CANcer is typically some form of androgen ablation and this results in quite satisfactory responses in

most men. However, once the disease is refractory to hormonal treatment, therapeutic success has been less readily achieved. In fact, it was just over a decade ago that the first demonstration of chemotherapy effectiveness was reported.[1] In that trial, mitoxantrone plus prednisone resulted in significantly better pain relief and quality of life when compared to prednisone alone, but no survival benefit was observed. Subsequently other chemotherapy agents and combinations were examined including docetaxel, and most were compared with mitoxantrone/prednisone.

One such trial was the TAX 327 study, an international, randomized trial for which data was initially published in 2004.[2] This trial compared docetaxel (75 mg/m2) administered every 3 weeks (D3), weekly docetaxel (10mg/m2) (D1), and mitoxantrone (12 mg/m2) (M), each with prednisone (5 mg orally, twice daily) (P), in 1,006 men with metastatic hormone-resistant prostate cancer. The original report was written at a time when there had been 557 deaths and the D3P treated patients had superior relief from pain, quality of life, reduction in PSA and survival, when compared to MP. The current report provides an update on the survival curves, now four years later.

Of the 1009 enrolled patients there were an additional 310 deaths that occurred in the interval bringing the total to 867 deaths. The survival benefit of D3P compared with MP has persisted with extended follow-up (P = .004). Median survival time was 19.2 months (95% CI, 17.5 to 21.3 months) in the D3P arm, 17.8 months (95% CI, 16.2 to 19.2 months) in the D1P arm, and 16.3 months (95% CI, 14.3 to 17.9 months) in the MP arm. More patients survived 3 years in the D3P and D1P arms (18.6% and 16.6%, respectively) compared with the MP arm (13.5%). Similar trends in survival between treatment arms were seen for men greater than and less than 65 years of age, for those with and without pain at baseline, and for those with baseline PSA greater than and less than the median value of 115 ng/mL.

COMMENTARY

The present analysis confirms that survival of men with metastatic hormone refractory prostate cancer is significantly longer after treatment with the three week docetaxel prednisone regimen (D3P) than with mitoxantrone prednisone. The results are, in fact, quite similar to the original report, with consistent improvement in pain and quality of life, as well as survival. It is also apparent that weekly docetaxel plus prednisone is not quite as effective in each of these parameters as the three week schedule. The added survival of approximately 3 months (D3P vs MP) is notable but many clinicians will be equally impressed with the differences in quality of life and pain relief. In fact, it remains unclear if asymptomatic patients with hormone refractory disease are better served by immediate chemotherapy or a delay until symptoms develop. Here again, we must rely on clinical judgment, matching patient goals and weighing survival advantage vs quality of life on and off chemotherapy. ■

References

1. Tannock IF, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol.* 1996;14(6):1756-1764.
2. Tannock IF, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351(15):1502-1512.

CME Questions

4. Raza and colleagues demonstrated that when lenalidomide was administered to patients with MDS but without 5q deletion, treatment resulted in:

a. no hematologic response
b. rapid improvement in neutropenia
c. reduced progression to AML
d. reduced need for red blood cell transfusion in a minority of patients

5. Bevacizumab administered in combination with interferon alfa for patients with metastatic renal carcinoma was shown to be:

a. prohibitively more toxic than interferon alone.
b. comparable in both toxicity and progression-free survival.
c. comparable with regard to toxicity but superior with regard to progression-free survival.
d. comparable with regard to toxicity but superior with regard to progression-free and overall survival.

6. Multivariate analysis of SEER data regarding adjuvant external beam radiation therapy for patients with pancreatic cancer has indicated:

a. no survival advantage.
b. survival advantage for only those with node negative disease.
c. survival advantage for those with locally exten-

sive or node positive disease, but not for those with node negative disease.
d. survival advantage for those with locally confined or extensive node negative or positive disease.

7. In the recent case-control breast cancer risk study having current or prior use of drugs in the statin class was associated with:

a. A significantly higher rate of breast cancer development.
b. A significantly lower risk of breast cancer development.
c. A modest reduction in breast cancer development, but only after 5 years of treatment.
d. None of the above.

8. The difference in median survival for patients with hormone refractory prostate cancer treated with docetaxel (at 3 week intervals) and prednisone compared to mitoxantrone and prednisone as reported from the TAX327 clinical trial is approximately:

a. 1.5 months
b. 3 months
c. 4.5 months
d. 6 months

Answers: 4 (d); 5 (c); 6 (d); 7 (d); 8 (b)

Free Gift for Subscribers

Readers of *Clinical Oncology Alert* who have recently subscribed or renewed their previous subscription have a free gift waiting. As a special bonus, *Clinical Oncology Alert* is offering free online reports to subscribers.

Those who are renewing their subscription can receive *Criteria for New Formulary Drugs*. New subscribers can receive *Clinical Briefs in Oncology*, a report which offers oncologists the most recent and important developments in the field.

Both reports are available online at www.ahcmedia.com. If you're accessing your online account for the first time, click on the "Activate Your Subscription" tab in the left-hand column. Then follow the easy steps under "Account Activation." After the login process is complete, the report is available at "Online Bonus Report."

If you have already activated your subscriber number and password at www.ahcpub.com, select the tab labeled "Subscriber Direct Connect to Online Newsletters. Please select an archive. . .". Choose your newsletter by the title from the dropdown menu and click "Sign on" from the left-hand column to log in. Then select "Online Bonus Report."

For assistance, call Customer Service at (800) 688-2421.

CME Objectives

The objectives of *Clinical Oncology Alert* are:

- to present the latest information regarding diagnosis and treatment of various types of cancer;
- 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:

Compliance Issues with Antiestrogen Therapy

PHARMACOLOGY WATCH

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

Another Study Implicates Avandia

In this issue: *Rosiglitazone (Avandia) implicated in yet another study; Prilosec and Nexium not associated with cardiac events; Anastrozole (Arimidex) shown more effective than tamoxifen for treatment of early-stage breast cancer; antibiotics show no effect on sinusitis; FDA actions.*

THE HANDWRITING MAY BE ON THE WALL FOR GlaxoSmithKline's rosiglitazone (Avandia) with yet another study implicating the drug with an increased risk of heart failure, cardiovascular events and mortality when compared to other oral hypoglycemic agents. The study was a nested case-control analysis of a retrospective cohort study using health care databases in Ontario. The patient population was nearly 160,000 older (>65 years of age) type 2 diabetics on at least one oral agent. The primary outcome was emergency visit or hospitalization for congestive heart failure, while secondary outcomes were AMI and all-cause mortality. After a mean follow-up of 3.8 years, monotherapy with rosiglitazone was associated with an increased risk of CHF (RR 1.60; 95% CI 2.10; *P*<.001), AMI (RR 1.40; 95% CI, 1.05-1.86; *P*=.02), and death (RR 1.29; 95% CI, 1.02-1.62; *P*=.03). Thiazolidinediones in general were evaluated in the study, but the adverse effects were limited to rosiglitazone. Adverse effects were found in patients who took the drug as a single agent or in combination with other hypoglycemic drugs (*JAMA*. 2007;298:2634-2643). Meanwhile, two large pharmacy benefit managers, Prime Therapeutics and HealthTrans, have dropped rosiglitzone from their formularies and the Department of Veterans Affairs is severely limiting the drug's use. Sales of the drug dropped 27% in the second quarter of 2007 and 39% in the third quarter.

Prilosec and Nexium Cleared

Omeprazole (Prilosec) and esomeprazole (Nexium) are not associated with increased rates of cardiac events, according to statements on the FDA web site. Concern was raised after AstraZeneca submitted data from two long-term studies in patients with severe gastroesophageal reflux to assess treatment with either drug vs surgery. Evaluation of secondary outcomes raised the question of whether long-term use of these drugs increased risk of cardiovascular events including sudden death. In a statement published on the FDA web site (www.fda.gov) on December 10, the agency states that it has completed a comprehensive scientific review of known safety data for both drugs. Based on review of the two studies presented by AstraZeneca and analysis of 14 comparative studies of omeprazole, no evidence of increased rate of cardiac events was seen. "Therefore, FDA continues to conclude that long-term use of these drugs is not likely to be associated with an increased risk of heart problems. The FDA recommends that health-care providers continue to prescribe, and patient's continue to use, these products as described in the labeling for the two drugs."

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) 262-5431. E-mail: iris.young@ahcmedia.com.

Anastrozole over Tamoxifen for Breast Cancer

Anastrozole (Arimidex) is more effective than tamoxifen as adjuvant treatment for early-stage breast cancer according to a study published online as an early release in the *Lancet Oncology*. The study looked at 6241 women with locally invasive breast cancer who were randomized to anastrozole or tamoxifen and followed for a median of 100 months. Primary endpoints were disease-free survival, and secondary endpoints were time to recurrence, incidence of new contralateral breast cancer, time to distant recurrence, overall survival, and death after recurrence. Endpoints were evaluated in the total population and in the hormone-receptor-positive subpopulation. The primary endpoint and all secondary endpoints favored anastrozole except for deaths after recurrence and overall survival for which there is no significant difference. Fracture rates were higher in patients receiving anastrozole compared to tamoxifen. There was no difference in cardiovascular morbidity or mortality between the two treatment groups. The authors conclude that the study "establishes long-term efficacy of anastrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with hormone sensitive, early breast cancer, and provide statistically significant evidence of a larger carryover effect after five years of adjuvant treatment with anastrozole." (*Lancet Oncology* early online publication, 50 December 2007).

Antibiotics and Steroids Not for Sinusitis

Antibiotics and topical nasal steroids are of no benefit for patients with acute maxillary sinusitis according to a new randomized controlled trial of 240 adults. Patients with acute non-recurrent sinusitis were randomized to treatment with antibiotics and nasal steroids, placebo antibiotic and nasal steroid, antibiotic and placebo nasal steroids, or placebo antibiotic and placebo nasal steroid. Amoxicillin 500 mg three times a day for seven days and budesonide spray once daily were the active drug use in the study. The main outcome was proportion of clinically cured at 10 days and the duration of symptoms. Antibiotics made no difference in the proportion of patients with symptoms lasting 10 days or more (29% with antibiotics, 33.6% with no antibiotics). Use of nasal steroid also made no difference for the same measure (31.4% with budesonide, 31.4% with no budesonide). The authors conclude that neither an antibiotic nor topical steroid alone or in combination was effective as the treatment for acute sinusitis in the primary care setting (*JAMA*. 2007;298:2487-2496).

FDA Actions

An expert advisory panel of the FDA has recommended against approving Merck's petition to take lovastatin (Mevacor) over-the-counter. This was the third request in 7 years for OTC status for the cholesterol-lowering drug. The advisers voted 10-2 against approval citing concerns whether patients were capable of determining if they are appropriate candidates for the medication. The FDA generally follows the advice of its advisory panels.

The FDA has approved yet another beta-blocker for the treatment of hypertension. MylanBertek's nebivolol (Bystolic) is a selective beta-1-adrenoreceptor blocker with vasodilating effects. The drug is the 19th beta-blocker approved in the United States.

Wyeth has received an approvable letter for bazedoxifene, a new selective estrogen receptor modulator (SERM) for the prevention of osteoporosis in postmenopausal women. In issuing the letter, the agency asked for more data on the risk of blood clots and stroke, problems that have plagued the other marketed SERM for this indication (raloxifene-Evista). The agency did not ask for new studies however. Wyeth is also seeking the indication for treatment of osteoporosis in postmenopausal women. When approved, bazedoxifene will be marketed as Viviant.

The FDA has issued a safety warning on fentanyl skin patches after several reports of deaths and life-threatening side effects associated with inappropriate use. The warning stresses that the patches are only for patients who are opioid-tolerant and have poorly controlled pain on other narcotic pain medications. The patches are not for postoperative pain or sudden or occasional pain. Patients who used the patch should be aware of the signs of fentanyl overdose. Patients and physicians should be aware of potential drug interactions and physicians and pharmacists need to instruct patients on appropriate use of the patch. Patients also need to be aware that heat sources such as heating pads, electric blankets, saunas, heated waterbeds, hot baths, sunbathing and even fever may result in sudden increases in blood levels of fentanyl.

The FDA has approved a new volume expander for the treatment of volume loss during surgery. German drugmaker Fresenius Kabi's Voluven utilizes a new synthetic starch that is insoluble in water. In clinical trials the product was found to be as safe and effective as Hespan, a currently approved starch solution volume expander. ■