Providing Evidence-based Clinical Information for 23 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.

Immediate Breast Reconstruction May Complicate Postmastectomy Radiotherapy

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Immediate breast reconstruction after mastectomy has intuitive appeal, but concern has been raised that such an approach hinders postmastectomy radiotherapy. In a retrospective review of 110 breast cancer patients who had immediate breast reconstruction this concern was quantified. Optimal therapy was achieved in approximately 50% of patients, falling far short of that achieved in a similar cohort who had not received immediate reconstruction (> 90%). Thus, for those who are considering breast reconstruction but for whom postmastectomy radiation is indicated, the findings from this study would suggest that delayed reconstruction would be the optimal. The findings, however, are derived from a single institution and by retrospective analysis. A similar approach examined in a multi-site prospective trial with clinical outcomes such as the incidence of local recurrence and overall survival would be valuable to establish the standards for which patients' immediate reconstruction is offered.*

Source: Motwani SB, et al. The impact of immediate breast reconstruction on the technical delivery of postmastectomy radiotherapy. *Int J Radiat Oncology Biol Phys.* 2006;66:76-82.

As reconstructive techniques are being perfected, many women are choosing to have immediate breast reconstructive surgery after mastectomy. This option has the advantages of superior cosmetic results, decreased surgical complications and cost, and a shorter combined recuperation time with one compared to two surgical procedures. In addition, there are psychological considerations inasmuch as it does not involve complete removal of the breast. Despite the appeal of this approach, there are concerns for those women for whom post-surgical radiation is planned.

In the current study, 110 breast cancer patients who were to undergo immediate breast reconstruction followed by radiotherapy at M.D.

VOLUME 23 • NUMBER 1 • JANUARY 2007 • PAGES 1-8

NOW AVAILABLE ONLINE
www.ahcmedia.com

Anderson Cancer Center between 1989 and 2003 were compared to contemporaneous stage-matched controls (n = 106) who had mastectomy without immediate reconstruction. A scoring system was used to assess optimal radiotherapy incorporating four parameters (one point each): breadth of chest wall coverage, treatment of the ipsilateral internal mammary chain, minimization of exposed lung, and avoidance of heart. An "optimal" plan achieved all objectives or a minor point deduction; "moderately" compromised treatment plans had 1.0 or 1.5 point deductions; and "major" had 2 or more point deductions.

In the immediate reconstruction group, due to anatomic considerations created by the surgical approach, changes in the radiation treatment protocol were required. In the current series, treatment plans were altered in 52% (33% moderately compromised, 19% severely compromised) compared to only 7% of the matched controls. In those who underwent immediate reconstructions, only 41 percent of the right-sided breast cancers and 51 percent of the left-sided cancers were considered to have optimal treatment compared with 92 percent of the right-sided and 94 percent of the left-sided cancers for the patients who had mastectomy without immediate reconstruction.

Furthermore, the immediate reconstruction with radiation group was found to have less satisfactory esthetic results, higher complication rates, and increase requirement for subsequent corrective surgeries.

COMMENTARY

Despite the intuitive value of immediate reconstruction, there appears to be a significant downside, particularly for those requiring postoperative radiation for optimal management. This report, although retrospective and not perfectly controlled, clearly demonstrates less than optimal treatment received by those who underwent immediate reconstruction compared to those who didn't. Presumably, this may affect local regional control and/or survival rates, although this remains to be demonstrated. The differences in achieving optimal treatment were so striking in this analysis that it is likely that detectable differences in clinical outcomes will become apparent with time. In the meantime, for patients with locally advanced breast cancer, the potential for compromised postmastectomy radiation treatment should be considered when deciding between immediate and delayed reconstruction. ■

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.
EDITORIAL GROUP HEAD: Lee Landenberger.
MARKETING PRODUCT MANAGER: Gerard Gernazian.
MANAGING EDITOR: Iris Williamson 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.

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
(Student/Resident rate: $120).
Multiple Copies
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.

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

Cognitive Decline and Adjuvant Breast Cancer Chemotherapy: A Matter of Dose?

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Breast cancer patients who received either high-dose, standard-dose or no chemotherapy were studied prospectively, utilizing a comprehensive battery of neuropsych tests. Compared to controls, only the group receiving the high-dose treatment experienced a deterioration in cognitive function.*

Source: Schagen SB, et al. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. *J Natl Cancer Inst.* 2006;98: 1742-1745.

For some, survival after cancer chemotherapy has been associated with a noted decline in cognitive function. Prior cross-sectional studies have supported the notion that chemotherapy may influence brain function in some patients.[1-3] In the current report from The Netherlands, a prospective analysis was performed. For this, two groups of breast cancer patients were randomized to receive either high-dose or standard-dose adjuvant chemotherapy and their cognitive function before and after therapy was assessed. A third group of breast cancer patients who received no chemotherapy and a group of women without breast cancer were similarly studied. The

latter two groups had cognitive assessments at a predefined interval of either 12 months (breast cancer no chemotherapy) or 6 months (control group). The neuropsychological testing consisted of ten tests comprising 24 test indices covering a wide range of cognitive domains.

The chemotherapy-treated patients were those who were considered high risk for recurrence. They were randomly assigned to receive either standard dose chemotherapy comprised of five monthly cycles of 5-fluorouracil (500 mg/m^2), epirubicin (90 mg/m^2) and cyclophosphamide (500 mg/m^2) followed by radiotherapy and tamoxifen (40 mg daily for 2-5 years) (FEC group; n = 39), or high-dose chemotherapy (four cycles of FEC, as above followed by one cycle of cyclophosphamide 6 gm/m^2, thiotepa 400 mg/m^2 and carboplatin 1.6 g/m^2 (CTC group; n = 28). There were 57 patients in the breast cancer/no chemotherapy group (no CT) and 60 women in the no breast cancer-control group.

At the first assessment, there were no detected differences among the four groups. However, more of the women treated in the CTC (high-dose) group experienced a decline in cognitive function over time than the control group (25% vs 6.7%; odds ratio [OR] = 5.3; 95% confidence interval [CI] = 1.3-21.2; P = 0.02). No such difference was observed for the FEC or the noCT groups (FEC vs control: OR = 2.2; 95% CI = 0.5-9.1; P = 0.27; noCT vs control: OR = 2.2; 95% CI = 0.6-8.0; P = 0.21). Repeated measures multiple analysis of covariance showed that deterioration in cognitive performance over time occurred across a variety of tests that measured cognitive functions. However, the measures that were sensitive to the so-called "executive function" exhibited the strongest effects.

COMMENTARY

The concept that chemotherapy may negatively influence higher brain function is well appreciated but neither the degree to which it occurs nor the population's most susceptible have been clearly established. The current report provides some important clues. The two different treatment groups were randomly assigned and, although the two additional control groups were quite different in several ways, there was no difference among the groups at the initial cognitive assessment. Only the group that received the high-dose regimen had a measurable deterioration. Those receiving standard-dose chemotherapy were no different than controls. This raises the possibility that either the specific drugs (thiotepa-tepa, etoposide and carboplatin) used in the high-dose group, or the actual dose intensity (eg, cyclophosphamide at 6 gm/m^2) resulted in impaired cognitive function. It would seem the latter is most likely. Yet, not all patients in the high-dose group had a measurable decline and it remains unclear which patients are vulnerable for this adverse outcome.

Thus, this well-constructed analysis provides prospective data confirming the findings of the earlier cross-sectional studies. Hopefully, future studies will identify those drugs, combinations or doses that are most dangerous in this regard and/or those constitutional features of some, but not all, cancer patients that make them particularly susceptible. ■

References

1. Van Dam FS, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *J Natl Cancer Inst.* 1998;90:210-218.
2. Ahles TA, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol.* 2002;20: 485-493.
3. Brezden CB, et al. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol.* 2000;18:2695-2701.

PET/CT-Colonography: One-Stop Colorectal Cancer Staging

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In 47 patients with newly diagnosed colorectal cancer, staging by combined CT and PET was compared to CT followed at a later time by PET or by CT alone. With regard to TNM staging, the combined CT/PET colonography proved more accurate than CT alone and was comparable in accuracy to CT and PET obtained on separate occasions. Thus, a single imaging protocol may become the standard staging approach once these findings are confirmed by more extensive trial.*

Source: Veit-Haibach P, et al. Diagnostic accuracy of colorectal cancer staging with whole-body PET/CT colonography. *JAMA*. 2006;296:2590-2600.

CLINICAL STAGING OF COLORECTAL CANCER IS performed to guide therapy. Typically, after colonoscopy, computerized tomography (CT) of the chest, abdomen and pelvis is obtained, and from this

a primary approach is formulated. Recently, there has been increased utilization of positron emission tomography (PET) in the initial staging as well. Whereas CT scans provide anatomic detail, PET displays functional information based upon metabolic activity and this has proven accurate for local and metastatic colorectal cancer.[1-4] The complimentary information provided by CT and PET has led to the commercial development of combined PET/CT scanners which offer the convenience of a one step staging procedure.

Veit-Haibach and colleagues throughout Germany have performed a prospective study of 47 patients with newly-diagnosed primary colorectal cancer to determine the staging accuracy of whole-body PET/CT colonography compared with the staging accuracies of CT followed by PET (CT+PET) and CT alone. On the day following colonoscopy, patients were examined by PET/CT colonography. The PET/CT colonography protocol included bowel relaxation/distension using scopolamine intravenous infusion and rectal water enema (2-3L at 37°C). Patients were followed for a mean of 447 days (range, 232-653 days).

The combined CT/PET colonography protocol correctly identified TNM stage in 74% of cases, whereas the sequential CT+PET was correct in 64% and CT alone (without PET) was correct in 52%. This 22% difference in accuracy between CT/PET compared to optimized CT alone proved statistically significant (P = .003). Examining the TNM characteristics of each patient, the gain in accuracy was primarily due to a greater precision in the T stage afforded by PET/CT compared to optimized CT alone. In contrast, there were no significant differences in assessing nodal (N) or distant metastatic (M) status among the three arms. With regard to nodal status, when a threshold for calling a node positive was 0.7 cm, CT alone was accurate 76% of the time (compared with PET/CT 86%), but when a 1 cm threshold was employed, the CT accuracy fell to 62% (ie, nodal status was under-staged in an additional 6 patients).

Of the 47 patients, therapy decisions were altered in 4 patients based upon the findings provided by the PET/CT protocol. For example, in one patient thought to have a single hepatic metastasis on the basis of conventional CT, a second small hepatic lesion was identified. Although this did not change the TNM stage, detection of the second lesion altered management to include a more extended surgical approach.

COMMENTARY

Thus, one may conclude from this report that a single stage PET/CT colonography protocol is a staging strategy worthy of consideration. It proved to be more accurate than an optimized CT protocol (without PET), particularly in assessing primary tumor (T) status, and was at least as accurate as CT followed separately by PET. Although a more accurate assessment of T status would seem of marginal importance in the primary management of colon cancer, for rectal cancer its potential value is more apparent. For example, a more precise determination of T status may help to select those who would benefit from neoadjuvant therapy compared with resection alone. Furthermore, accurate assessment of tumor size may aid in determining the optimal surgical approach (eg, laparotomy, laparoscopy, or transanally).

Compared to sequential CT followed on a later occasion by PET, the accuracy was at least equivalent and the added value of the combined protocol would relate to the convenience of a single procedure and more timely results. Questions that warrant further clarification relate to the overall technical feasibility and costs incurred by performing PET on all preoperative colorectal patients. If the data support utilization of PET in the staging of colorectal cancer patients, then it would make sense that a single PET/CT colonography approach should be implemented. ■

References

1. Rohren EM, et al. Clinical applications of PET in oncology. *Radiology*. 2004;231:305-332.
2. Kalff V, et al. The clinical impact of (18)F-FDG PET in patients with suspected or confirmed recurrence of colorectal cancer: a prospective study. *J Nucl Med*. 2002;43:492-499.
3. Huebner RH, et al. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. *J Nucl Med*. 2000;41:1177-1189.
4. Antoch G, et al. Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. *J Clin Oncol*. 2004;22: 4357-4368.

Thalidomide Maintenance after Tandem Transplants Improves Survival in Myeloma

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD, MS

Section of Hematology/Oncology, University of Chicago

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

Synopsis: *An increasing number of active therapies have become available for multiple myeloma in addition to high dose chemotherapy followed by autologous transplant (ASCT). This three-arm randomized trial compared, to pamidronate, to thalidomide and pamidronate, against no therapy as maintenance after a second ASCT. In the 597 randomized patients, all younger than 65 years of age, responses (CR + VGPR) were better in the thalidomide maintenance arm at 67% (P= 0.03) compared to 55 to 57% in the other cohorts. OS was also better at 87%, compared to 74 to 77% in the other groups (P < 0.04). Pamidronate did not reduce skeletal events. Thalidomide maintenance improved responses and survival in younger patients after tandem autologous transplant.*

Source: Michel Attal, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108:3289-3294.

The therapeutic landscape for multiple myeloma has changed dramatically over the past decade from limited choices to an "embarrassment or riches." High-dose chemotherapy followed by autologous stem cell rescue (ASCT) plays a central role in eligible patients. It has a clear survival benefit, although the timing of ASCT, the need for single or double ASCT, and the value of maintenance treatment remain clinical challenges.[1,2] Further, new agents such as thalidomide, lenalidomide, and bortezomib have considerable activity and the combination of various agents may enhance responses. Despite these advances, relapses eventually occur in most patients, even after ASCT. Maintenance therapy after ASCT is one strategy to prolong responses or even eradicate the malignant clone. Prior studies on maintenance have been hampered by agents exhibiting modest activity, such as interferon or corticosteroids.

In this trial, Attal and colleagues evaluated maintenance thalidomide therapy after tandem ASCT. Between 2000 and 2003, the French intergroup enrolled 1019 patients younger than 65 years of age from 74 centers on two consecutive myeloma trials. Inclusion required at least one of two adverse prognostic factors of elevated Beta-2-microglobulin or deletion of chromosome 13. Induction therapy consisted of continuous infusion VAD (vincristine, doxorubicin and dexamethasone) every 3 weeks for 3 to 4 cycles. Patients with a preserved performance status underwent tandem ASCT after high dose melphalan chemotherapy using 140 mg/m^2 before the first ASCT and 200 mg/m^2 before the second ASCT.

Two months after the second ASCT, the 597 (77%) patients without progressive disease were randomized to one of three arms: no maintenance (group A), pamidronate monthly (group B), pamidronate monthly and thalidomide at 400 mg daily (group C) without thromboembolic prophylaxis. Thalidomide was discontinued due to toxicity in 39% at a median of 8 months. Thrombosis was rare and did not differ among groups.

At randomization (after tandem ASCT), the response rates prior to maintenance were similar across study arms at 47% to 50% CR/VGPR (very good partial response) and 39% to 42% PR. The thalidomide arm showed the best improvement in CR, enabling 67% to achieve a CR/VGPR compared to 55% in arm A and 57% in arm B (P = 0.03). The thalidomide cohort also experienced improved relapse-free survival (P = 0.003) and overall survival (P = 0.04). The actuarial four year survival was 75% (70%-82%) without thalidomide and 87% (80%-93%) with thalidomide after randomization. Salvage therapies and survival after relapse were fairly similar at about 73% to 78% at one year after relapse. Although the survival benefit persisted in most subgroups, thalidomide did not appear to afford a survival benefit for baseline deletion of chromosome 13 (P = 0.2) and those in CR at randomization. Skeletal events appeared similar in all arms at 24% in group A, 21%, in Group B, and 18% in Group C (P = 0.4).

COMMENTARY

This well-designed trial demonstrates a benefit in responses and overall survival for thalidomide maintenance after tandem ASCT. The results contrast with another recently published study by Barlogie and colleagues using thalidomide and tandem ASCT. In that randomized study, active treatment entailed thalidomide not only for maintenance

but also during the entire period before and after ASCT. Thalidomide was continued until toxicity or disease progression. Thalidomide improved response rates and event free-survival but did not benefit overall survival.[3] The difference may relate to increased toxicity of administering thalidomide during chemotherapy.

Thalidomide tolerance is a major issue as the drug may lead to somnolence, fatigue, constipation, peripheral neuropathy and venous thrombosis. It was reassuring that using thalidomide, the thrombosis risks was low, even without prophylaxis. Presumably, this relates to administering it as monotherapy as opposed to during other chemotherapy and/or corticosteroids, where the risk may be higher. Nevertheless, 39% discontinued the drug due to peripheral neuropathy and the mean dose used was 200 mg/day for a mean of 15 months, indicating the 400 mg starting dose frequently required reduction.

Several additional limitations must be considered. First, induction therapy consisted of VAD. Whether the use of other more active agents for induction will mitigate the benefit of thalidomide maintenance after ASCT can not be determined. Second, a tandem ASCT is often reserved for incomplete responses or progression after the first ASCT. Should thalidomide maintenance have a role after a first ASCT when the second ASCT is not immediately planned? Finally, the results, albeit positive, also underscore limitations in efficacy of this approach. The survival curve did not "plateau," implying tumor control, rather than complete eradication, and the subset harboring a deletion of chromosome 13 did not appear to benefit.

The results clearly point to alternative strategies of testing agents that have a better toxicity profile and activity against deletion of chromosome 13 such as lenalidomide and bortezomib.[4] The promising findings also suggest it is a viable strategy to incorporate active agents and high-dose chemotherapy with autologous transplant to improve outcome. ■

References

1. Attal M, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med.* 1996;335:91-97.
2. Blade J, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood*. 2005;106:3755-3759.
3. Barlogie B, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med*. 2006;354:1021-1030.
4. Richardson PG, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med*. 2003;348:2609-2617.

Chemotherapy for Unknown Primary: A Phase II Trial

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Optimal treatment for carcinoma of unknown primary has not been established. In a multicenter, randomized Phase II trial, 66 patients were treated with cisplatin, gemcitabine and either paclitaxel or vinorelbine. The regimens were well tolerated and the observed response rates approached 50%. Response duration and median time to progression were comparable between the two treatments, but the overall survival of 13.6 months for the vinorelbine-containing regimen compared to 9.6 months for the paclitaxel-containing regimen) and its slightly better tolerability led these investigators to favor that regimen for promotion to large scale trial.*

Source: Palmeri S, et al. Cisplatin and gemcitabine with either vinorelbine or paclitaxel in the treatment of carcinomas of unknown primary site. Results of an Italian multicenter, randomized, Phase II Study. *Cancer*. 2006;107: 2898-2905.

Despite advances in imaging and pathology techniques, slightly less than 5% of all cancers present as metastatic disease from clinically unrecognized primaries.[1] This obviously heterogeneous group represents a challenge for oncologists and there currently is no established standard of care. In the current report, two somewhat different treatment regimens were compared in a randomized, multicenter trial conducted by the Unknown Primary Italian Study Group. Sixty-six previously untreated patients with carcinomas of unknown primaries (CUP) were randomized to receive Cisplatin (35 mg/m^2), gemcitabine (1000 mg/m^2) and either paclitaxel (70 mg/m^2) (CGT) or vinorelbine (25 mg/m^2) (CGV) on days 1 and 8 of 21-day cycles. Twenty-nine (44%) presented with 2 or more involved

sites, and histopathology was adenocarcinoma in 73% and squamous in 11%. For all patients, the search for a primary site included routine but extensive imaging studies and endoscopy, as indicated.

For the 33 patients who received the paclitaxel-containing regimen (CGT), 16 (48.5%) experienced an objective response and 9 (27.2%) had stable disease. In comparison, for those 33 patients who received the vinorelbine-containing regimen (CGV), 14 patients (42.3%) experienced an objective response and 8 (24.2%) patients had disease stabilization. The median response duration and the median time to progression were similar in both treatment groups. The median overall survival (OS) was 9.6 months (95% confidence interval [CI], 7.11-12.09 months) for patients who received CGT and 13.6 months (95% CI, 6.61-20.59 months) for those who received CGV. Grade 3 and 4 toxicities were more frequent in the paclitaxel-containing (CGT) arm. The authors, based upon the marginal differences described in overall survival and lesser toxicity, favor the CGV regimen for future examination in Phase III studies.

COMMENTARY

It is clear that we have not reached a satisfactory regimen for the effective treatment of metastatic carcinoma of unknown primary. Several trials have been published (nicely reviewed in the current report) and most report response rates in the 25-40% range with median overall survivals of approximately 6-10 months. CGT falls right in this range, whereas CGV might be a little better, at least on the basis the observed median overall survival of 13.6 months is among the best ever reported for carcinomas of unknown primary. In general, conclusions regarding overall survival are not typically made from phase II trial inasmuch as patient selection in relatively small studies can easily exaggerate such measures. This is particularly dangerous for a heterogeneous group, such as those with carcinoma of unknown primary. Thus, despite appropriate randomization methodology, potentially having non-comparable groups renders a comparison of CGT vs CGV (or either, with published reports in the literature), risky. For example, it is known that metastatic disease involving the liver is more ominous than other sites (eg, lymph nodes or bone).[1, 2] Other factors such as sex, gender, performance status, number of sites involved, and histology are also predictive of outcome and it would not be possible, outside of a large-scale study, to provide adequate trial design to definitively establish the superiority of CGV or other regimen when compared to those others with comparable (but slightly lesser) results in phase II investigation.

That stated, the data from this trial and from the literature would support the inclusion of each of the agents in future studies. A number of published trials have focused on platinum analogues[3,4] and on taxanes[5,6], both of which, it would seem, improve response rates but not necessarily overall survival. Gemcitabine, because of its broad spectrum of activity and favorable toxicity profile, is a logical drug for investigation in this setting.[7] Similarly, vinorelbine has demonstrable activity in patients with lung, breast, head/neck, ovarian and uterine carcinomas, and also an acceptable toxicity profile.[8] With the data presented in this report, outside of a clinical trial, the CGV regimen would seem as logical a choice as any for the treatment of newly diagnosed patients with metastatic carcinoma from unknown primary.

References

1. Pavlidis N, et al. Cancer of unknown primary (CUP). *Crit Rev Oncol Hematol.* 2005;54:243-250.
2. Hess KR, et al. Classification and regression tree analysis of 1000 consecutive patients with unknown primary carcinoma. *Clin Cancer Res.* 1999;5: 3403-3410.
3. Milliken ST, et al. Metastatic adenocarcinoma of unknown primary site. A randomized study of two combination chemotherapy regimens. *Eur J Cancer Clin Oncol.* 1987;23:1645-1650.
4. Eagean RT, et al. Lack of value for cisplatin added to mitomycin-doxorubicin combination chemotherapy for carcinoma of unknown primary site. A randomized trial. *Am J Clin Oncol.* 1987;10:82-85.
5. Greco FA, et al. Carcinoma of unknown primary site. *Cancer.* 2000;89:2655-2660.
6. Greco FA, et al. Carcinoma of unknown primary site: sequential treatment with paclitaxel/carboplatin/ etoposide and gemcitabine/irinotecan: a Minnie Pearl Cancer Research Network phase II trial. *Oncologist*. 2004;9:644-652.
7. Hainsworth JD, et al. Combination chemotherapy with gemcitabine and irinotecan in patients with previously treated carcinoma of an unknown primary site: a Minnie Pearl Cancer Research Network Phase II trial. *Cancer.* 2005;104:1992-1997.
8. Gridelli C, Shepherd FA. Chemotherapy for elderly patients with non-small cell lung cancer: a review of the evidence. *Chest.* 2005;128:947-957.

CME Questions

1. **The chance of having suboptimal radiation delivered as a result of immediate breast reconstruction after mastectomy is approximately:**
   a. 10%.
   b. 25%.
   c. 50%.
   d. 75%.

2. **In the assessment of cognitive function in breast cancer patients, which groups of patients had significant decline when compared to controls?**
   a. Those receiving standard-dose chemotherapy.
   b. Those receiving high-dose chemotherapy.
   c. Those receiving no chemotherapy.
   d. All of the above.
   e. None of the above.

3. **In the staging of primary colorectal cancer, PET/CT colonography proved more accurate than CT, particularly in which component of the TNM classification system.**
   a. T
   b. N
   c. M
   d. All of the above
   e. None of the above

4. **In this trial, what did thalidomide maintenance after tandem autologous transplant for myeloma provide?**
   a. Improved overall survival
   b. A significant increase risk in deep venous thrombosis
   c. Decreased response rate
   d. Long-term cure for myeloma harboring deletion of chromosome 13

Answers: 1 (c); 2 (b); 3 (a); 4 (a)

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:

Myeloma Treatment Stratgies

Dear *Clinical Oncology Alert* Subscriber:

This issue of your newsletter marks the start of a new continuing medical education (CME) semester and provides us with an opportunity to review the procedures.

Clinical Oncology Alert, sponsored by AHC Media LLC, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours - the best possible patient care.

The objectives of *Clinical Oncology Alert* are to:

- 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.

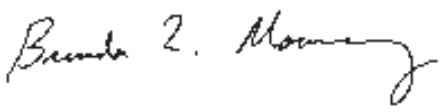
Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers against the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

At the end of each semester you will receive an evaluation form to complete and return in an envelope we will provide. Please make sure you sign the attestation verifying that you have completed the activity as designed. Once we have received your completed evaluation form we will mail you a letter of credit. This activity is valid 36 months from the date of publication. The target audience for this activity is oncologists.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5560. You can also email us at: customerservice@ahcmedia.com.

On behalf of AHC Media, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,



Brenda Mooney
Senior Vice-President/Group Publisher
AHC Media LLC

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.

Study: Long-Term Use of Clopidogrel for DES Patients

Patients with coronary artery disease who have received intra-coronary, drug-eluding stents (DES) may benefit from longer courses of clopidogrel than is currently standard. Researchers at Duke looked at 4,666 patients undergoing percutaneous coronary interventions with bare metal stents (BMS) (n = 365) or DES (n = 1501). Patients were followed up at 6, 12, and 24 months with the main outcomes being death, non-fatal MI, and the composite of death or MI at 24-month follow-up. For patients who received DES and were event free at 6 months, use of clopidogrel was a significant predictor of fewer events at 24 months (death rate 2.0% with clopidogrel vs 5.3% without , P = 0.3; death/MI 3.1% vs 7.2%, P = 0.02). However the same was not seen for BMS patients, with no significant difference in death rate or death/MI in the patients who took clopidogrel. For DES patients who were event free at 12 months, use of clopidogrel continued to improve outcomes (death rate 0% with clopidogrel versus 3.5% without, P = .004; death/MI 0% versus 4.5%, $P <$ 0.001). For patients with BMS who were event free at 12 months, use of clopidogrel was still not associated with any change in death rate (3.3% vs 2.7% P = 0.57) or death/MI (4.7% 3.6%, P = 0.44). The authors conclude that extended use of clopidogrel in patients with drug-eluding stents may reduce the rate of death and MI. However the appropriate duration of clopidogrel administration has not yet been determined. (*JAMA* early release article posted 12/05/06). Implications of the study are significant in that current recommendations following PCI with drug eluting stents is for 3 to 6 months of clopidogrel. Several studies have shown that these stents have increase risk of catastrophic stent thrombosis, higher than bare metal stents, months after the procedure. This has led some experts to recommend long-term use of clopidogrel, perhaps even lifetime use in patients who have received a DES. While the study does not make recommendations, it does confirm the fact that clopidogrel is beneficial for patients who received a DES for up to 2 years.

Drug Labels — A Prescription for Misunderstanding?

Prescription drug labels are commonly misunderstood according to a new study in the *Annals of Internal Medicine*. Nearly 400 English-speaking patients were enrolled in the study to assess their understanding of 5 different medication labels, all had relatively common instructions. Patients with low literacy, defined as 6th-grade level or less, were less likely to understand all 5 labels. Patients with low literacy read the instruction, "Take two tablets by mouth twice daily," but only 35% could demonstrate the number of pills to be taken daily. Patients who had multiple prescriptions were significantly

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: jennifer.corbett@ahcmedia.com.

more likely to misunderstand prescription labels. The authors admit that the patient's actual drug-taking behaviors were not observed, so authors could not demonstrate a link between misunderstanding the labels and actual medication errors. Still the authors suggest that patients of all ages would benefit from additional efforts to improve the clarity of prescription labels and suggest that the text and format of existing prescription containers should be redesigned and standardized (*Ann Int Med*. 2006;145: Epub ahead of print).

Osteonecrosis of the Jaw — New Side-Effect to Bisphosphate Use

With the widespread use of bisphosphonates for the prevention and treatment of osteoporosis, a new side effect, osteonecrosis of the jaw, has emerged as a concern. A new "Perspective" piece in the *New England Journal of Medicine* (November 30) helps answer the question, "Osteonecrosis of the Jaw—Do Bisphosphonates Pose a Risk?" Osteonecrosis of the jaw is characterized by exposed bone in the mandible, maxilla, or palate, and is often associated with dental disease, dental surgery, oral trauma, periodontitis, and poor dental hygiene. The author points out that the first case of osteonecrosis associated with bisphosphonates was reported in 2003, nearly 10 years after the drugs were first approved. Most reported cases are associated with high-dose intravenous bisphosphonates given to control metastatic bone disease where the rate is reported from 1.3% to 7%. The average patient with osteonecrosis had been receiving intravenous bisphosphonate therapy for 1.5 to 3 years. Use of oral bisphosphonates to treat osteoporosis involves doses that are often 10 times lower than intravenous doses. Fewer than 50 cases of osteonecrosis of the jaw have been associated with oral bisphosphonates, or approximately 1 in 100,000 patient years. There is concern that with long-term use of oral bisphosphonates, the rate of osteonecrosis may increase in the future. Some have even suggested that osteoporosis patients take a "drug holiday" after 5 years of therapy to reduce the risk; however, the benefit of the strategy is unclear at this time. A routine dental evaluation is reasonable prior to starting bisphosphonates; however, there is no reason to stop the drugs prior to dental treatment. Some oral surgeons advocate temporarily withholding drugs if invasive dental care is needed, but given the very long half-life of these drugs, it is unclear whether temporary cessation will have any effect on reducing the risk of osteonecrosis, and more research is needed (*N Eng J Med*. 2006; 355:2278-2281).

Beta-Blockers and Depression — Unlinked?

Many physicians are cautious about the use of beta-blockers after myocardial infarction because of the risk of depression. A new study suggests that this concern may be unwarranted. Researchers from the Netherlands looked at 127 patients who had a myocardial infarction and were not taking beta-blockers versus 254 MI patients who were taking beta-blockers at 3, 6, and 12 months post MI. Outcomes were scores on 2 commonly used depression scales. No significant differences were found between beta-blocker users and non-beta-blocker users regarding the presence of depressive symptoms or depressive disorder, although a trend towards more depression was seen in patients with long-term use of beta-blockers and patients on higher doses. Use of a hydrophilic versus lipophilic beta blocker made no significant difference. The authors conclude that in post MI patients, use of beta-blockers is not associated with an increase in depressive symptoms or depressive disorders in the first year (*J Am Coll Cardio*. 2006;48:2209-2214).

FDA Actions

The FDA has approved telbivudine for the treatment of chronic hepatitis B virus (HBV) infections in adults. The drug is approved for patients with evidence of viral complication in either persistent elevations in serum transaminases or histologically active disease. The approval was based on a one-year study, and more than 1,300 patients showed significant decreases in HBV-virus DNA levels compared with lamivudine. Telbivudine, which is given as a 600 mg oral daily dose, will be marketed by Idenix Pharmaceuticals and Novartis as "Tyzeka."

FDA has approved the first generic version of ondansetron injection (Zofran) for the prevention of nausea and vomiting associated with chemotherapy and prevention of postoperative nausea and vomiting. The generic product will be manufactured by Teva and SICOR Pharmaceuticals. GlaxoSmithKline, which previously held the patent for Zofran, had 2005 sales of nearly $850 million.

The FDA has approved expanded use of Herceptin for HER2-positive, early-stage breast cancer after mastectomy or lumpectomy. Previously, the drug was only approved for HER2-positive, metastatic breast cancer. ■