AMERICAN HEALTH CONSULTANTS®

CLINICAL ONCOLOGY ALERT

A monthly update of developments in cancer treatment and research

Providing Evidence Based Clinical Information for 15 Years

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

Radiotherapy for Lentigo Maligna Melanoma

ABSTRACT & COMMENTARY

Source: Schmid-Wendtner MH, et al. *J Am Acad Dermatol* 2000;43:477-482.

The most important therapeutic part of melanoma treatment is adequate surgical excision. Randomized clinical trials have shown the importance of larger surgical margins as the Breslow's depth increases. For many melanomas that occur on the face, the required wide local excision may result in unacceptable cosmetic or functional morbidity. An alternative would be the use of radiation therapy.

In this report from Germany, 22 patients with lentigo maligna melanoma were treated with radiation therapy. The patients' ages ranged from 58 to 87 years old (median 76) of whom 86% were female. Although sites of involvement included the eyelid, nose, scalp, or ear, the most common site was the cheek (45%). The Breslow's depth ranged from 0.1 to 10 mm with a median of 0.35 mm.

Treatment consisted of surgical excision of the nodular part of the lesion. The remaining lentiginous part of the lesion was then radiated using a direct field and a 0.5 to 2.0 cm safety margin of clinically normal skin. The total dose was 100 Gy given in 10 fractions and the treatment was given with a 14.5 kv machine. The study also included 42 patients successfully radiated for benign lentigo maligna, not otherwise discussed herein.

Patients were treated between 1987 and 1998 with a mean follow-up time of 23 months. Nineteen of the 22 patients with melanoma remained in complete remission. Two patients had a local recurrence after 13 and 44 months, both of whom were successfully salvaged by surgical excision. The last patient developed pulmonary metastases 44 months after therapy with no evidence of a local failure. This patient's melanoma was 3.6 mm deep. Cosmetic results were described as good or excellent in all patients. No serious complications were seen.

Volume 15 • Number 11 • November 2000 • Pages 81-88

COMMENT BY KENNETH W. KOTZ, MD

Of the different clinical subtypes of melanoma, lentigo maligna melanoma is the least common, accounting for 5% of melanoma lesions.[1] Compared with other subtypes, it also presents later in life with a mean age of diagnosis in the eighth decade.[1] It is typically located on the nose, cheeks, or temples and may have been present for years in the precursor form, lentigo maligna. However, prognosis and treatment are no different than any similarly staged melanoma.

Even with the use of Moh's surgery, the proximity of facial melanomas to critical structures may preclude surgical intervention. Thus, this report of long-term control with the use of radiation therapy is welcome. Of note, there is no reason why primary treatment with radiation therapy could not be preceded by a sentinel lymph node biopsy, if indicated. However, readers of *Clinical Oncology Alert* may recall the recent discussion of the unique problems which occur when a sentinel node biopsy is attempted in patients with melanoma of the head and neck.[2]

Although complete surgical excision remains the standard of care, this series of 22 cases of lentigo maligna melanoma demonstrates that fractionated radiotherapy may be a reasonable alternative to surgery in locations of cosmetic or functional importance. Of course, the good results may be related in part to the underlying excellent prognosis of these early stage patients, most of whom had stage I or II disease. The relatively nonpenetrating radiation used in this study deposits half of its intensity by the time the beams have penetrated only 1 mm of tissue.[3] With a relative sparing of the normal tissues located only a few millimeters deep, this approach may work more through the desquamation of several layers of cells rather than direct radiotoxicity.[3]

More conventional radiation would involve electron beams with 6-18 MeV rather than the 14.5 kv orthovoltage radiotherapy used in this study. Furthermore, conventional treatment in the United States with megavoltage equipment implies a somewhat lower total dose, and dose per fraction. As might be expected, high rates of control with lentigo maligna melanoma have been reported with conventional treatment.[3] Altogether, the report by Schmid-Wendtner demonstrates that radiation therapy is a safe and effective alternative for melanoma of the head and neck, in particular lentigo maligna melanoma, when surgical excision cannot be performed. ❖

References

1. Langley R. In: Balch C, et al, eds. *Cuteaneous Melanoma*. 3rd ed. St. Louis, Mo: Quality Medical Publishing; 1998:81-101.
2. Kotz K. *Clinical Oncology Alert* 2000;4:26-27.
3. Cooper J. *Hematol Oncol Clin North Am* 1998;12: 849-863.

Clinical Oncology Alert, ISSN 0886-7186, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.
EDITORIAL GROUP HEAD: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
ASSOCIATE MANAGING EDITOR: Robin Mason.
COPY EDITOR: Robert Kimball.

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

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

Back issues: $37.
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.

AMERICAN HEALTH CONSULTANTS™
THOMSON HEALTHCARE

Subscriber Information
Customer Service: 1-800-688-2421
Customer Service E-Mail Address:
customerservice@ahcpub.com
Editorial E-Mail Address:
robert.kimball@ahcpub.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices
United States
$269 per year (Student/Resident rate: $105).
Multiple Copies
1-9 additional copies: $197 each; 10 or more copies: $175 each.
Canada
Add GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation
American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 20 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

For CME credits, add $50.

Questions & Comments
Please call Robin Mason, Associate Managing Editor, at (404) 262-5517 or Robert Kimball, Copy Editor, at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure
In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Ershler is on the speaker's bureau for Wyeth and does research for Ortho Biotech. Dr. Roberts is a contractor for Eli Lilly and Agouron and is a consultant for Novartis Pharmaceuticals. Dr. Kotz serves on the speaker's bureau of Rhône-Poulenc Rorer. Dr. Albertini is involved in research for Powder Ject vaccines, Inc and Lexigen Pharmaceuticals.

Toxicities of Androgen Deprivation

ABSTRACT & COMMENTARY

Synopsis: *Asymptomatic men at risk for clinical recurrence of prostate cancer who elect androgen deprivation therapy experience fatigue, increased sexual problems, and a decline in overall quality of life.*

Source: Herr H, O'Sullivan M. *J Urol* 2000;163: 1743-1746.

Quality of life in asymptomatic men at risk for clinical progression of prostate cancer was

observed following a decision between immediate and deferred androgen deprivation. Subjects either had extracapsular extension (T3) or an increased or rising prostrate-specific antigen (PSA) following surgery or radiation. Subjects were recruited from a support group conducted by Herr and O'Sullivan, and were predominantly well educated, active, married, white men in their late sixtes. Seventy-nine men (31 without prior local therapy) chose immediate treatment, and 65 men (29 without prior local therapy) deferred treatment. Among men choosing immediate treatment, 16 underwent orchiectomy, 41 received leuprolide alone, and 22 received leuprolide and flutamide. Quality of life was evaluated three times over one year using three previously validated quality-of-life instruments. Multiple comparisons were made and conservative statistical criteria for significance were applied ($P < 0.007$ was considered significant; $P < 0.05$, a trend). There were no significant differences in demographics or baseline quality-of-life scores between men who chose immediate or deferred treatment.

Men choosing immediate androgen deprivation reported significantly worse status with regard to fatigue, sexual problems, and the quality of life uniscale, and trends toward worse status with regard to physical function and psychological distress. Among men choosing treatment, men choosing orchiectomy reported significantly less fatigue than men choosing leuprolide with or without flutamide.

COMMENT BY JOHN D. ROBERTS, MD

This report reminds us that in asymptomatic men androgen deprivation has an adverse effect upon quality of life. Post-treatment PSA surveillance labels increasing numbers of asymptomatic men as harboring incurable prostate cancer. These men must make decisions concerning the timing of androgen deprivation in the absence of definitive information concerning survival, or disease-related morbidity differences between immediate vs. delayed treatment. There also has been little information concerning treatment-related morbidity. This report indicates that treatment-related morbidity is multi-dimensional, but the structure of the report does not provide any clinical "feel" for the magnitude of the problems. Clinicians skeptical of the benefits of early androgen deprivation will find further support in a previous report in which six of 16 men surviving for longer than 60 months after orchiectomy experienced osteoporotic fractures.[1] ❖

Reference

1. Daniel H. *J Urol* 1997;157:439-444.

Tamoxifen and Endometrial Cancer: How Bad is the Risk?

ABSTRACT & COMMENTARY

Synopsis: *Endometrial cancer is known to occur in tamoxifen-treated patients. In this case-control analysis from The Netherlands, the relative risk for endometrial cancer was found to be 1.5 (95%; CI 1.1-2.0) and the risk rose to 6.9 for those using it for five or more years. This is consistent with other reports. However, unlike earlier reports, stage at presentation, histology, prognostic factors, and endometrial cancer survival were all less favorable for those with a history of tamoxifen use. Still, the risks were small compared to the benefits of tamoxifen for breast cancer patients, but concerns were raised for its more generalized use for breast cancer prevention.*

Source: Bergman L, et al. *Lancet* 2000;356:881-887.

There is an increased risk of endometrial cancer with tamoxifen treatment, however the actual risk had not previously been established. Recently, Bergman and colleagues from the Comprehensive Cancer Center's ALERT Group performed a nationwide (in The Netherlands) case-control study on the risk and prognosis of endometrial cancer in approximately 1200 treated breast cancer patients (309 who had developed endometrial cancer and 860 matched controls). Tamoxifen had been used by 36% of those with endometrial cases and 28.5% of the controls. Thus, the relative risk (RR) of endometrial cancer was 1.5 (95%; CI 1.1-2.0). The RR rose with more prolonged use of tamoxifen, reaching 2.0 (1.2-3.2) for those using the drug for 2-5 years and 6.9 (2.4-19.4) for those using it for five or more years.

Furthermore, long-time users were more likely to have mesodermal tumors or sarcomas, p53-positive tumors, and be estrogen receptor negative. The three-year endometrial cancer survival rate was worse for long-term tamoxifen users than non-users (76% for > 5 years, 85% for 2-5 years, vs 94% for nonusers, [$P = 0.02$]).

COMMENT BY WILLIAM B. ERSHLER, MD

Clinicians have long been aware of the increased risk of endometrial cancer in tamoxifen-treated breast cancer

patients,[1] and this well constructed investigation revealed no unexpected findings in that regard. Indeed, the observed RRs were what might have been predicted from other series[2,3] in which the RR had been posited as approximately four for those tamoxifen users older than the age of 50. However, the important and unexpected finding in the Dutch study was that the tumors that developed in the tamoxifen-treated women were of more, not less, aggressive histology; and survival was worse when compared to that for women without prior tamoxifen use. This runs contrary to the predictions based upon the NSABP-B14 trial data[1] in which the endometrial cancers that developed were mostly low-grade, easy to diagnose, and uncomplicated to treat.

Are there ready explanations to account for these findings? Perhaps the fact that the patients included in this analysis included some diagnosed as early as the 1970s, at a time when the awareness of the increased risks was incomplete, reducing the chance of early detection. Also, the tamoxifen-endometrial cancer association was recognized primarily from clinical trials (such as the NSABP B-14 trial), and surveillance might be more comprehensive under these more controlled circumstances. Thus, earlier detection, in more modern series, might explain the discrepancy in stage at presentation and it may be that the advanced stage at presentation of endometrial cancer in tamoxifen-treated patients will be less likely observed in current series. Nonetheless, the more aggressive histologies observed, and the greater likelihood of increased p53 expression (a negative prognostic factor) are hard to write off. Clearly there is a lot we don't understand about the influence of tamoxifen (or other steroids for that matter) on uterine tissue and malignant transformation.

These findings are significant, but the risk of endometrial cancer, even with the more malignant features, remains less than the irrefutable benefit for breast cancer patients in reducing recurrence and preventing contralateral breast disease. However, concerns are raised for the more widespread use in women without breast cancer for the purpose of cancer prevention. The common application of such an approach should await the analysis of the current large breast cancer prevention trials. Also, it is possible that other, more selective (i.e., with reduced uterine effect) estrogen response modifiers will be shown to have less or no increased risk for endometrial cancer. ❖

References

1. Fisher B, et al. *J Natl Cancer Inst* 1994;86:527-537.
2. Mignotte H, et al. *Int J Cancer* 1998;76:325-330.
3. Fisher B, et al. *J Natl Cancer Inst* 1998;90:1371-1388.

Recurrent Thromboembolic and Bleeding Complications in Cancer Patients

ABSTRACT & COMMENTARY

Synopsis: *A retrospective analysis of 1303 eligible patients (264 with malignancy) was performed to assess the incidence of venous thromboembolic recurrences and major bleeding complications during oral anticoagulant therapy with vitamin K antagonists among patients with venous thromboembolism. Patients with known malignancy had an increased incidence of recurrent thromboembolism (27.1 vs 9.0/100 patient-years) as well as an increased incidence of major bleeding episodes (13.3 vs 2.1/100 patient-years), when compared with patients without known malignancy. The incidence of thromboembolic episodes was lower when the INR was above 2.0 compared with below 2.0. While vitamin K antagonists are effective in patients with known malignancy, these patients have an increased incidence of thrombotic and bleeding complications compared with patients without known malignancy.*

Source: Hutten BA, et al. *J Clin Oncol* 2000;18: 3078-3083.

The clinical manifestation of venous thromboembolism, including deep-venous thrombosis and pulmonary embolism, is well known to occur in patients with cancer.[1] Standard treatment for venous thromboembolism includes initial heparinization followed by vitamin K antagonists and is similar both in cancer patients and in patients without cancer.[1,2] The initial heparinization can be accomplished either with unfractionated heparins or with low-molecular weight heparins.[3,4] Potential advantages of the low-molecular weight heparins include the ability to have subcutaneous administration without laboratory monitoring, thus allowing for the possibility for out-of-hospital treatment. Several studies have demonstrated the safety of low-molecular weight heparins for patients with venous thromboembolism. The initiation of oral anticoagulant therapy with one of the coumarins, vitamin K antagonists, that are used for the long-term treatment of patients with venous thromboembolism, will usually begin within 24 hours of initial heparin treatment.[2] Warfarin is the most commonly used coumarin in North America, while other coumarins such as acenocoumarol are used in some European countries.[2] The unfractionated heparin or low-molecular weight heparin will be continued for at least

four days following initiation of warfarin therapy, and the heparin therapy is usually discontinued when treatment with warfarin has resulted in an increase in the international normalized ratio (INR) of greater than 2.0 for two consecutive days.[1,2] Treatment with warfarin will then usually continue for 3-6 months with a target INR of 2.0-3.0. Well-recognized complications during this period of oral anticoagulant therapy include bleeding and recurrent thrombosis.[1,2,5]

Hutten and colleagues report a retrospective analysis of 1303 eligible patients (264 with malignancy) who were treated with heparin (unfractionated or low-molecular weight) and vitamin K antagonists started within one day of heparin therapy and continued for three months, with a target INR of 2.0-3.0. The patients in this retrospective analysis were involved in one of two open, multicenter, randomized clinical trials evaluating the safety, efficacy, and cost-effectiveness of unfractionated heparin vs. low-molecular weight heparin for patients with symptomatic proximal deep venous thrombosis[3] or objectively documented deep venous thrombosis and/or pulmonary embolism.[6] The patients with cancer were older on average than the patient without cancer (mean age ± SD of 66 ± 13 vs 59 ± 17, respectively). Cancer diagnoses of the patients with cancer included cancers of the genitourinary tract (29%), the gastrointestinal tract (19%), and the breast (15%). A small, but statistically significant difference was present for percentage of time spent within a therapeutic INR range between 2.0-3.0 between patients with and without cancer (50% vs 54% respectively, $P = 0.005$). A total of 35 recurrent episodes of venous thromboembolism (31 deep venous thromboses and 4 pulmonary embolisms) occurred during treatment with vitamin K antagonists (14 among patients with cancer and 21 among patients without a known cancer diagnosis). The calculated incidence of recurrent venous thromboembolism in patients with cancer was 27.1 per 100 patient-years and was greater than the 9.0 per 100 patient-years incidence in patients without a known cancer diagnosis (rate ratio 3.0; 95% CI, 1.5-5.9; $P = 0.003$). The highest incidence of recurrent venous thromboembolism for both patients with and without cancer occurred during periods with an INR below 2.0.

The overall incidence of major bleeding complications was also compared between patients with and without a known cancer diagnosis. A total of 12 major bleeding complications occurred, with seven among patients with cancer and five among patients without a known cancer diagnosis. The calculated incidence of major bleeding complications in patients with cancer was 13.3 per 100 patient-years and was greater than the 2.1 per 100 patient-years incidence in patients without a known cancer diagnosis (rate ratio 6.2; 95% CI, 2.0-19.7; $P = 0.002$). Surprisingly, while the highest incidence of major bleeding complications in patients without a cancer diagnosis occurred as expected in the INR range over 3.0, this same pattern of excess bleeding risk during times with an INR above 3.0 was not seen in the cancer patients. It was suggested that the small number of patients with major bleeding events in the different INR categories may result in a low precision for the analysis of bleeding complications as a function of INR.

COMMENT BY MARK R. ALBERTINI, MD

Recurrent venous thromboembolism and major bleeding complications are important considerations during therapy of patients with vitamin K antagonists for venous thromboembolism. The results from this study provide quantitative estimates of this risk for patients both with and without a cancer diagnosis. While the data analysis for this study was retrospective, the patients were well characterized and had been previously entered into two large clinical studies. Thus, important insight is provided into the magnitude of this problem for patients with cancer. Cancer patients are clearly identified as a high-risk group for recurrent venous thromboembolism and major bleeding during therapy with vitamin K antagonists for venous thromboembolism. Close monitoring for these complications is needed.

The current monitoring of these patients includes blood sample monitoring to achieve time within a therapeutic INR range between 2.0-3.0. It is suggested that more frequent monitoring of high-risk patients to achieve a greater percentage of time in the therapeutic INR range would be useful. However, the burden of increased monitoring for cancer patients also requires consideration. Alternate treatment strategies of venous thromboembolism for this patient population, such as additional investigation of low-molecular weight heparins as well as development of new anticoagulants, may prove useful.[7] Clinical investigation of new management strategies is needed. Until these trials are conducted and evaluated, it is important to recognize cancer patients as a high-risk group for the complications of recurrent venous thromboembolism and major bleeding complications during treatment with vitamin K antagonists for venous thromboembolism. ❖

References

1. Prandoni P, et al. *Ann Intern Med* 1996;25:1-7.
2. Ginsberg JS. *N Engl J Med* 1996;335:1816-1828.
3. Koopman MM, et al. *N Engl J Med* 1996;334:682-687.

4. Levine M, et al. *N Engl J Med* 1996;334:677-681.
5. Van der Meer FJ, et al. *Arch Intern Med* 1993;153: 1557-1562.
6. The Columbus Investigators. *N Engl J Med* 1997;337: 657-662.
7. Bauer KA. *J Clin Oncol* 2000;18:3065-3067.

Improved Treatment for Metastatic Colorectal Cancer

ABSTRACT & COMMENTARY

Synopsis: *A prospective, randomized study involving 683 patients with metastatic colorectal cancer was performed to compare combination chemotherapy with irinotecan (125 mg/m^2), fluorouracil (500 mg/m^2), and leucovorin (20 mg/m^2) weekly for four weeks every six weeks (231 patients) with fluorouracil (425 mg/m^2) and leucovorin (20 mg/m^2) daily for five consecutive days every four weeks (226 patients). A third group of patients received irinotecan alone (125 mg/m^2) weekly for four weeks every six weeks (226 patients). The weekly treatment with irinotecan plus fluorouracil and leucovorin was shown to be superior to the regimen of fluorouracil and leucovorin in terms of progression-free and overall survival, and did not compromise the quality of life.*

Source: Saltz LB, et al. *N Engl J Med* 2000;343: 905-914.

Metastatic colorectal cancer remains an important public health problem in the United States and is estimated to account for 10% of cancer deaths in men and 11% of cancer deaths in women in the year 2000.[1] The primary, initial treatment for patients with this disease has included the antimetabolite fluorouracil (5-FU), which works as an inhibitor of the enzyme thymidylate synthase. Several strategies for biochemical modulation of 5-FU have been evaluated, including administration of 5-FU in combination with leucovorin, a reduced folate (tetrahydrofolate) to increase the affinity of 5-FU for thymidylate synthase.[2,3] Various schedules of 5-FU and leucovorin have been evaluated, and this treatment combination is frequently administered as an initial therapy for patients with metastatic colorectal cancer. Other agents, such as irinotecan, have also been evaluated for patients with metastatic colorectal cancer. Irinotecan works as a potent inhibitor of topoisomerse I, and has been shown to have activity for patients with metastatic colorectal cancer.[4-6] In addition, clinical investigations have identified dose and schedules for combination therapies involving irinotecan in combination with 5-FU and lecovorin for patients with metastatic colorectal cancer, and efficacy of this treatment has been suggested.[7,8]

Saltz and colleagues performed a phase-3 trial to compare combination chemotherapy with irinotecan, 5-FU, and leucovorin with a commonly used regimen of 5-FU and leucovorin as initial treatment for patients with metastatic colorectal cancer. A third group of patients was assigned to receive irinotecan alone. A total of 683 patients were enrolled into this prospective, randomized, multi-center trial. The intent-to-treat patient distribution included 231 patients in the group assigned irinotecan, 5-FU, and leucovorin, 226 patients in the group assigned 5-FU and leucovorin, and 226 patients in the group assigned irinotecan alone. Baseline patient characteristics were similar in treatment groups except for an increased percentage of men in the three-drug group vs. the two-drug group (65% vs 54%; $P = 0.02$). The primary study end point was progression-free survival, and this was significantly longer in the patients assigned to receive irinotecan, 5-FU, and leucovorin than in the patients assigned to receive 5-FU and leucovorin (median of 7.0 months vs 4.3 months; $P = 0.004$). The median progression-free survival in the patients assigned to receive irinotecan alone was 4.2 months and was similar to patients receiving 5-FU and leucovorin. Objective response rates were also greater in patients assigned irinotecan, 5-FU, and leucovorin than in patients assigned 5-FU and leucovorin (50% vs 28%; $P < 0.001$). The objective response rate in patients assigned irinotecan alone was 29% and was similar to patients assigned 5-FU and leucovorin. Finally, overall survival was also increased in patients assigned irinotecan, 5-FU, and leucovorin in comparison with 5-FU and leucovorin (median survival of 14.8 months compared to 12.6 months; $P = 0.04$). The median survival of patients assigned irinotecan alone was 12.0 months and was similar to the 12.6 months of patients assigned to 5-FU and leucovorin.

An analysis of adverse effects was performed for patients who received each of the three treatments. The adverse effects of grade-3 diarrhea and grade-3 or 4 vomiting were greater in the irinotecan, 5-FU, and leucovorin group compared with the 5-FU and leucovorin group. The adverse effects of grade-3 or 4 mucositis, grade-4 neutropenia, and neutropenic complications were greater in the 5-FU and leucovorin group compared with the irinotecan, 5-FU, and leucovorin group. Grade 4 diarrhea was similar in both the 3-drug and 2-

drug groups. Overall quality of life analyses showed no significant differences between the treatment groups given irinotecan, 5-FU, and leucovorin or 5-FU and leucovorin. Saltz et al conclude that the treatment combination of irinotecan, 5-FU, and leucovorin, when compared with a commonly used regimen of 5-FU and leucovorin, is associated with higher rates of tumor regression, progression-free survival, and overall survival without compromising quality of life.

COMMENT BY MARK R. ALBERTINI, MD

Treatment options are improving for patients with metastatic colorectal cancer. The use of biochemical modulation of 5-FU with leucovorin provided a recent advance, and has been widely used as first-line treatment for patients with metastatic colorectal cancer. Additional agents with distinct mechanisms of anti-tumor activity, such as the topoisomerase I inhibitor irinotecan, have been shown to have activity against metastatic colorectal cancer. The current study by Saltz et al provides a prospective, randomized evaluation of combination chemotherapy with irinotecan, 5-FU, and leucovorin in comparison with 5-FU and leucovorin. A control arm of irinotecan alone is also evaluated. Saltz et al confirm the importance of prognostic factors including good performance status, fewer metastatic sites, normal lactate dehydrogenase and bilirubin levels, normal white-cell count, and a hemoglobin level more than 11 g/dL with better outcomes. The demonstration of improved tumor regression, increased progression-free and overall survival, and no compromise in quality of life with irinotecan, 5-FU, and leucovorin represents an important advance for the treatment of patients with metastatic colorectal cancer. This overall survival benefit is especially noteworthy as Saltz et al report that more than half of patients initially randomized to 5-FU and leucovorin received irinotecan as second-line therapy upon subsequent disease progression. Thus, concurrent first-line treatment with irinotecan, 5-FU, and lecovorin appears better than sequential administration of irinotecan following failure of first-line treatment with 5-FU and leucovorin.

The current report describes an advance for our treatment of patients with metastatic colorectal cancer. Further treatment advances for patients with metastatic colorectal cancer are certainly needed and, perhaps, will be identified as additional agents receive clinical investigation. However, an even greater effect for the current regimen of irinotecan, 5-FU, and leucovorin may be possible as adjuvant therapy for patients with resected stage-3 disease. Saltz et al report that a clinical trial evaluating this combination treatment for patients with resected stage-3 disease is now in progress, and results from that study are eagerly awaited. ❖

References

1. Greenlee RT, et al. *CA Cancer J Clin* 2000;50:7-33.
2. Buroker TR, et al. *J Clin Oncol* 1994;12:14-20.
3. Leichman CG, et al. *J Clin Oncol* 1995;13:1303-1311.
4. Conti JA, et al. *J Clin Oncol* 1993;11:909-913.
5. Rougier P, et al. *J Clin Oncol* 1997;15:251-260.
6. Cunningham D, et al. *Lancet* 1998;352:1413-1418.
7. Saltz LB, et al. *J Clin Oncol* 1996;14:2959-2967.
8. Douillard JY, et al. *Lancet* 2000;355:1041-1047.

CME Questions

19. Which of the following statements about the complications of recurrent thromboembolic and bleeding complications during therapy with vitamin K antagonists is true for patients with cancer?

a. Thrombotic complications are most likely during times when the INR is less than 2.0.
b. Thrombotic complications are most likely during times when the INR is between 2.0 and 3.0.
c. Thrombotic complications are most likely during times when the INR is greater that 3.0.
d. The likelihood of thrombotic complications is independent of the measured INR.

20. Which of the following is true regarding the study by Schmid-Wendtner and radiation for melanoma?

a. Radiation can be an alternative in lentigo maligna melanoma but not lentigo maligna.
b. Radiation is only effective in lentigo maligna melanoma if the total dose is 100 Gy.
c. A sentinel lymph node biopsy cannot be performed if radiation of a melanoma is planned.
d. Lentigo maligna melanoma presents later in life compared with other subtypes of melanoma.

21. Which of the following statements is *incorrect* about irinotecan, 5-FU, and leucovorin as compared with a commonly used regimen of 5-FU and leucovorin for first-line treatment of patients with metastatic colorectal cancer?

a. Higher rates of tumor regression occur with the three-drug regimen.
b. Progression-free survival is improved with the three-drug regimen.
c. Quality of life is lower with the three-drug regimen.
d. Overall survival is improved with the three-drug regimen.

22. Which of the following statements regarding tamoxifen use for the treatment of breast cancer and the development of endometrial cancer is true?

a. There is an increased risk of endometrial cancer that increases with duration of tamoxifen treatment but the developed endometrial cancers have more favorable histological features and are more likely curable than de novo endometrial cancer.
b. There is an increased risk of endometrial cancer that appears independent of duration of tamoxifen treatment but the devel-

oped endometrial cancers have more favorable histological features and are more likely curable than de novo endometrial cancer.

c. There is an increased risk of endometrial cancer that increases with duration of tamoxifen treatment and the developed endometrial cancers have less favorable histological features and are less likely curable than de novo endometrial cancer.

d. There is an increased risk of endometrial cancer that appears independent of duration of tamoxifen treatment and the developed endometrial cancers have less favorable histological features and are less likely curable than de novo endometrial cancer.

23. Androgen deprivation is associated with:

a. no measurable adverse effects.
b. hair loss.
c. an increase in fatigue.
d. prolonged survival in asymptomatic prostate cancer.

Annual Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Clinical Oncology Alert	0 8 8 6 - 7 1 8 6	10/18/00
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$219.00

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: Willie Redmond; Telephone: 404/262-5448

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)*: Donald R. Johnston, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*: Rob Kimball, same as above

Managing Editor *(Name and Complete Mailing Address)*: Glen Harris, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Medical Economics Data, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:

13. Publication Name: Clinical Oncology Alert — 14. Issue Date for Circulation Data Below: November 2000

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1961	1864
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	1689	1664
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	0	0
	(4)	Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			1689	1664
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	0	0
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			16	16
f. Total Free Distribution *(Sum of 15d and 15e)*			16	16
g. Total Distribution *(Sum of 15c and 15f)*			1705	1680
h. Copies Not Distributed			256	184
i. Total *(Sum of 15g. and h.*			1961	1864
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			99	99

16. Publication of Statement of Ownership
Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 10/18/00

Donald R. Johnston

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

In Future Issues:

Taxanes in Gastric Cancer