AMERICAN HEALTH CONSULTANTS

CLINICAL ONCOLOGY ALERT

Providing Evidence-based Clinical Information for 16 Years

A monthly update of developments in cancer treatment and research

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

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

Long-term Survival Following Induction Chemoradiotherapy and Esophagectomy for Esophageal Carcinoma

ABSTRACT & COMMENTARY

Synopsis: Forty-four esophageal cancer patients participated in a phase II trial of induction with 5-fluorouracil, cisplatin, interferon alpha2b, and external beam radiotherapy prior to esophagectomy. Seventeen patients were alive at a median follow-up time of 50 months and 15 of these had no evidence of disease. Among the 14 patients with > 3 years survival, 12 had no evidence of disease. Although clinical parameters measured were not associated with long-term survival, in this data analysis, a lack of a p53 mutation revealed a trend to longer survival. In summary, further support is provided that multimodal neoadjuvant therapy may affect a cure for esophageal cancer. Moreover, it is concluded that recurrence is unlikely for those patients undergoing this neoadjuvant regimen who survive for 3 years or longer.

Source: Lew JI, et al. *Arch Surg*. 2001;136:737-742.

Five years have passed since the publication of the first larger phase III trial examining neoadjuvant chemoradiotherapy for esophageal carcinoma.[1] Despite this promising earlier study, with 3-year survival rates increased from 6% to 32% in the treatment arm, subsequent phase III trials from other institutions did not achieve the same significantly positive results.[2,3] However, given the grim prognosis and increasing incidence of esophageal tumors,[4] investigators continue to pursue refinement of neoadjuvant treatment regimens as the best hope for cure.

In the current study, Lew and colleagues built upon previously published work[5,6] to report "long-term survivor" (> 3 years) data and to identify clinical parameters associated with long-term survival, among a cohort with stage I-IV resectable adeno- or squamous cell carcinoma of the esophagus. Forty-four patients without evidence of metastatic disease and with American Heart Association performance status of 0-1, Eastern Cooperative Oncology Group performance status of 0-2, and normal hepatic,

Volume 16 • Number 11 • November 2001 • Pages 81-88

INSIDE

renal, and hematologic serology values were initially enrolled. Patients with documented tracheobronchial tree or mediastinal involvement were excluded. Pretreatment evaluation included an extensive search for metastases, including pre- and posttreatment CT staging, later reviewed by single radiologist who was blinded to posttreatment pathologic stage. In order to reduce inpatient length of stay, the induction regimen changed from 28 days of 5-fluorouracil (5FU), cisplatin, and interferon alpha2b with concurrent 40 Gy external beam radiation (n = 16) to 21 days of a similar regimen with 45 Gy of radiation (n = 28).

Thirty-six patients underwent curative resection (33 transhiatal esophagectomy; 3 with additional thoracotomy) among the 41 patients who completed the neoadjuvant course. Pathologic review of resected specimens revealed 10 "complete responders" (24%), that is, patients without evidence of residual disease after therapy. Twenty-three more patients (56%), termed "partial responders" in a definition much more rigorous than that used traditionally, had only microscopic disease in resected or nodal tissue. Remaining patients had gross residual tumor and were characterized as having "no response."

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.
MANAGING EDITOR: Robin Mason.
ASSOCIATE MANAGING EDITOR: Neill Larmore
SENIOR 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, Managing Editor, at (404) 262-5517 or Robert Kimball, Senior 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. Albertini does research for Powder Ject vaccines, Inc and Lexigen Pharmaceuticals. Drs. Hawkins, Kaplan, Kotz, and Morris report no relationships related to this field of study. Drs. Canellos, Chabner, Einhorn, Goodman, Lippman, Pinedo, and Sutton did not return financial disclosures.

At a median follow-up time of 50 months, 17 patients were alive and 15 were without evidence of disease. Fourteen patients were "long-term survivors" and 12 of these were disease-free (median follow-up = 54 months, median survival not yet reached). Seven long-term survivors had a complete pathologic response; 6 of these remained disease-free. The other 7 long-term survivors had a partial response; again, 6 remained disease-free. Lew et al maintain that complete vs. partial pathologic response was not correlated with long-term survival.

In order to examine the value of clinical variables in predicting long-term survivorship, age, sex, 28-day vs. 21-day treatment regimen, clinical tumor stage, clinical nodal stage, and p53 mutation status were examined. Ten patients among the 14 long-term survivors had no p53 mutations; 1 was mutated. The remaining 3 may be inferred over-expressors based on previously published data.[5] Lew et al found no statistically significant association between the variables listed and survival. They did note that lack of p53 mutation was associated with a trend to longer survival, but they neither supplied a supporting *P* value nor reported p53 results in a table that demonstrated the other potential predictor variables.

In summary, 33 of 41 patients (80%) with stage I-IV esophageal carcinoma who completed this neoadjuvant regimen had a major pathologic response. Seventeen of 44 patients enrolled (39%) were alive at a median follow-up of 50 months and 14 of 44 (32%) survived > 3 years, supporting Lew et al's contention that multimodal therapy can cure esophageal carcinoma. Lew et al concluded that none of the clinical parameters were predictive of long-term survival, although lack of p53 mutation was suggestive. They further concluded that recurrence is unlikely for patients undergoing this regimen who survive > 3 years, noting that only 2 of 14 long-term survivors (14%) had recurred by a median follow-up time of > 54 months.

COMMENT BY ARDEN MORRIS, MD

Esophageal carcinoma continues to be an aggressive malignancy with 5-year survival rates of 5-15%, providing impetus to resolve ongoing controversies about therapy modalities and to better predict effective treatment. As in the current phase II study, most investigators pool the histologic subtypes, adeno- and squamous-cell carcinoma, both because the mainstay of treatment continues to be anatomically based surgical resection and because adequately powered studies have been elusive. However, evidence suggests that histology may predict differing responses to chemotherapy.[7] Furthermore, while the incidence of squamous cell carcinoma is in

decline, the incidence of adenocarcinoma has been increasing steadily over the past 25 years.[4] Among larger published phase III trials comparing neoadjuvant chemoradiotherapy to surgery alone, the first, including adenocarcinoma patients only, demonstrated a significant survival benefit with neoadjuvant therapy at 3 years.[1] A second trial, including only squamous cell carcinoma patients, demonstrated no overall survival benefit but increased disease-free survival.[3] Interestingly, this study used only cisplatin and no 5FU in the chemotherapy regimen, and used only 18.5 Gy of radiation. Historically, phase II studies have shown inconsistent or no benefit when less than 40 Gy radiation was used.[8,9] An additional phase III trial of neoadjuvant therapy for esophageal squamous cell carcinoma showed no benefit after using 20 Gy radiotherapy.[10] A more recent phase III trial included both histologic types, used 5FU, cisplatin, and vinblastine with 45Gy concurrent radiotherapy.[2] Survival at 3 years was 16% in the surgery-only arm and 30% in the neoadjuvant arm, but at a median follow-up of 8.2 years, no significant survival difference could be detected. Clearly, reliable determination of patient and tumor characteristics indicating the most effective treatment regimens will require further stratification based on tumor histology.

Lew et al describe the encouraging discovery of no residual tumor in 24% of resected specimens after neoadjuvant chemoradiotherapy. This finding of complete response, consistent with other phase II and phase III trials, has led some investigators to question the use of performing a potentially highly morbid esophagectomy.[11,12] Lew et al argue that available imaging modalities cannot separate complete responders from those with only microscopic disease (56% in this study), and therefore locoregional control continues to mandate resection. Indeed, clinical staging has repeatedly been < 30% accurate in studies which included histologic comparison.[1,8,9] Lew et al could have bolstered their argument by reporting results from their single radiologist who retrospectively provided CT staging while blinded to pathologic results.

Although presence of a complete response in the resected specimen does not guarantee a cure, previous studies using more than 40 Gy radiotherapy have indicated a significant association with or at least a trend toward longer survival.[1,13] The current study reports a lack of association between complete pathologic response and long-term survival, despite 7 of 10 complete responders (70%) going on to > 3 year survival while only 7 of 23 partial responders (30%) enjoyed > 3 year survival. A p-value is not provided by Lew et al but, by Fischer's exact test, $P = 0.057$. Regardless of complete response status, patients will continue to require systemic treatment, but if complete response enhances prognosis, it should certainly continue to be a goal.

Those who argue for trials including nonresection treatment arms will surely agree that more accurate predictors of complete response must be identified. In previously published work from this cohort, p53 mutation correlated positively with residual disease, disease-free interval, and survival.[5] The current study examined lack of p53 mutation and long-term survival, reporting no significant association but a trend toward improved survival. Because data provided are incomplete, no *P* value can be determined by the reader. Another esophageal carcinoma study of biological markers predicting response to neoadjuvant therapy found that p53 was nonprognostic.[14] However, Lew et al determined that c-erb B-2 showed a significant favorable association and may prove a fruitful area for future research.

In conclusion, Lew et al have provided further interim data about their cohort of esophageal carcinoma patients subjected to neoadjuvant chemoradiotherapy, especially focusing on patients surviving > 3 years. They add to the literature supporting better outcomes for patients undergoing neoadjuvant therapy but, although data were gathered prospectively, fail to provide a solid denominator of all patients presenting with disease that might allow conclusions to be drawn more accurately. No correlation between the clinicopathologic parameters measured (age, sex, 28-day vs 21-day treatment regimen, clinical tumor stage, clinical nodal stage, and p53 mutation status) and long-term survival were identified, reassuringly in the case of the change in treatment regimen. Ultimately, Lew et al presented excellent clinical results for their 32% long-term survivors (median survival > 54 months) and advocated effectively for ongoing resection, but were unable to identify clinical correlates of long-term survival. ❖

References

1. Walsh T, et al. *N Engl J Med*. 1996;335:462-467.
2. Urba SG, et al. *J Clin Oncol*. 2001;19:305-313.
3. Bosset JF, et al. *N Engl J Med*. 1997;337:161-167.
4. Blot WJ, et al. *JAMA*. 1991;265:1287-1289.
5. Ribiero U, et al. *Cancer*. 1998;83:7-18.
6. Posner MC, et al. *Cancer J Sci Am*. 1998;4:237-246.
7. Wolfe WG, et al. *J Thorac Cardiovasc Surg*. 1993;105: 749-755.
8. Terz JJ, et al. *Surgery*. 1993;114:71-75.
9. Hoff SJ, et al. *Ann Thorac Surg*. 1993;56:282-287.
10. LePrise EL, et al. *Cancer*. 1994;73:1779-1784.
11. al-Sarraf M, et al. *J Clin Oncol*. 1997;15:277-284.
12. Coia LR, et al. *J Clin Oncol*. 2000;18:455-462.

13. Forastiere AA, et al. *J Clin Oncol*. 1993;11:1118-1123.
14. Duyhaylongsod FG, et al. *Ann Surg*. 1995;221(6): 677-683.

Stereotactic Radiosurgery Boost Can Increase Survival in Patients with Brain Metastases

ABSTRACT & COMMENTARY

Synopsis: During the past several decades, the Radiation Therapy Oncology Group (RTOG) has sponsored trials aimed at finding radiotherapy dose and fractionation schedules that improved median survival in brain metastases patients. Unfortunately, little progress was made. This study evaluated retrospective, pooled data from 10 institutions comparing overall survival in patients that received a stereotactic radiosurgery (SRS) boost to RTOG historical controls treated with whole brain radiotherapy (WBRT) alone. They concluded that a SRS boost confers a statistically significant improvement in OS across all 3 stratified groups tested.

Source: Sanghavi SN, et al. *Int J Radiat Oncol Biol Phys*. 2001;51:426-434.

There is a dearth of randomized data relating to the effect of SRS on overall survival in patients with brain metastases. Although retrospective data do suggest a survival advantage, selection bias may be a confounding factor. While previous work, like the Patchell randomized study,[1] has shown us that local resection of solitary metastases can improve survival when combined with WBRT, it is unclear whether SRS can offer an analogous benefit through a minimally invasive technique. Sanghavi and colleagues from 10 institutions set out to analyze their data on 973 SRS patients in order to determine whether median survival in SRS patients is extended beyond what is typically seen after palliative WBRT. After eliminating those patients who did not receive WBRT prior to SRS, did not receive a SRS boost to all visible residual lesions, did not have complete follow-up data, underwent resection of metastases, or were treated for salvage of recurrences in the brain, there were 502 evaluable patients.

In order to overcome problems analyzing their patient population with its diverse prognostic characteristics, Sanghavi et al borrowed the 3-tiered classification schema for patients with brain metastases previously published by Gaspar,[2] and assigned all of their patients to the corresponding groups. This schema was derived using recursive partitioning. Class I patients were those with a Karnofsky Performance Score (KPS) > 70, < 65 years of age, with no active disease at the primary tumor site and no evidence of systemic metastases. Class III patients had a KPS < 70, and Class II patients represented everyone else. Then Sanghavi et al used the patients from the 3 previously published RTOG whole brain radiotherapy trials analyzed and sorted by Gaspar for comparison purposes. Those trials were conducted between 1976 and 1993.

The pooled SRS study patients could have any KPS, primary tumor histology, number of brain metastases, size of brain metastases, age, comorbidities, history of chemotherapy, and dose of WBRT and SRS. Both methods of SRS boosting, either with a gamma knife or linear accelerator, were acceptable. Median age for the entire group was 59 years (r = 26-83), and 52% were male. Median KPS was 80, and only 7% (n = 34) had a KPS < 70 (Class III). Fifty-six percent (n = 279) of patients had lung cancer metastatic to brain, 21% had malignant melanoma, 12% had breast cancer, and the remainder were unspecified. Sixty-four percent (n = 320) of patients had their primary tumors controlled, and 57% (n = 285) had systemic metastases. There were 112 patients in Class I (22%), 356 in Class II (71%), and 34 in Class III (7%). The median number of patients contributed per institution was 46 (r = 11-99). Three institutions administered SRS boosts with a gamma knife, 6 with a linear accelerator, and 1 with both. One hundred and seventy-seven patients were treated on a gamma knife, and 325 on a linear accelerator. Median follow-up for alive patients was 37 months (r = 2-133). The demographics between the SRS study group and the RTOG historical controls were similar, except for a higher median KPS in the current study.

Survival was measured from the first treatment day. Median overall survival (OS) for the entire group was 10.7 months. Median OS for Class I was 16.1 months, Class II = 10.3 months, and Class III = 8.7 months. Survival comparisons with the RTOG database were carried out for each prognostic class using variance estimates. Univariate and multivariate analyses yielded the same statistically significant independent prognostic factors: KPS, primary tumors that were controlled, and absence of systemic metastases ($P < .002$). After adjusting for prognostic class, no significant differences were found by treating institution, and no differences were found by method of SRS boost. For all 3

classes, SRS prolonged median survival compared with the RTOG controls, who received WBRT alone. The RTOG patients survived a median of 7.1 months for Class I, 4.2 months for Class II, and 2.3 months for Class III ($P < .05$).

Sanghavi et al concluded that their study showed promising findings that should be evaluated in a randomized trial. While there was a significant benefit seen in all 3 prognostic categories, the patients in the lowest category, KPS < 70, showed the most marked increase in OS. Given these results, and notwithstanding the lack of randomized data, Sanghavi et al recommended SRS as an excellent, relatively noninvasive, alternative for brain metastases patients who are not surgical candidates.

■ COMMENT BY EDWARD J. KAPLAN, MD

This study is especially interesting, not only because it reports the largest published experience on the use of SRS in patients with brain metastases, but because Sanghavi et al stratified their patients using previously published criteria based on recursive partitioning. Recursive partitioning analysis (RPA) is founded on statistical clustering, and its goal is to identify groups or classes that are homogeneous in terms of survival. This appears to be a logical tool to use when dealing with the hodgepodge of patients that present with brain metastases. Sanghavi et al point out that 1 potential pitfall of this model as adapted from Gaspar was that it does not take into account the number of brain metastases per patient. Sanghavi et al feel that this is problematic, and is as yet an unresolved issue. Another questionable aspect of the study was the use of the RTOG patients as historical controls. Shanghavi et al cite "time-shifting" as a possible source of bias, whereby differences in diagnostic and therapeutic resources available during the respective study periods may have skewed the outcome in favor of the more modern study population. This seems to be a real possibility.

Sanghavi et al report that preliminary data from a recent RTOG randomized trial comparing WBRT to WBRT + SRS boost show an improvement in local control, but no difference in OS for patients with 2-3 lesions. Data on patients with solitary brain metastases have not yet been reported. Unfortunately, there were relatively low numbers of patients in each arm and high numbers of protocol violations, so the results may not be conclusive.

For the many brain metastases patients who are not surgical candidates, SRS boosting with either a linear accelerator or gamma knife helps establish improved local control, and may confer a survival benefit. Confirmatory studies are needed to verify the results of this pooled data analysis. ❖

References

1. Patchell R, et al. *N Engl J Med*. 1990;332:494-500.
2. Gaspar L, et al. *Int J Radiat Oncol Biol Phys*. 1997;37: 745-751.

Controversy Revisited: The Role for Nephrectomy in Metastatic Renal-Cell Carcinoma

ABSTRACT & COMMENTARY

Synopsis: In an EORTC trial, good performance status patients presenting with metastatic renal cell carcinoma were treated with either nephrectomy plus interferon or interferon alone. Complete response rate and overall survival was better for the surgically treated group.

Source: Mickisch GHC, et al. *Lancet*. 2001;358: 966-970.

At the time of diagnosis, about 20% of patients with renal carcinoma will have evidence for distant metastases and 25% have locally advanced disease. Of those with resectable lesions and no evidence for metastatic disease who are treated with nephrectomy, approximately one third will develop distant metastases.[1,2] Treatment of metastatic disease with chemotherapy has not been satisfactory, and new immunotherapies, although only marginally better, are considered standard care.[3]

The role of nephrectomy for those who present with metastatic disease has been controversial.[4] The purpose of this study was to establish whether radical nephrectomy done before interferon-based immunotherapy improved time to progression and overall survival compared with interferon alone for those who present with primary renal carcinoma and measurable metastatic disease.

The multi-site trial was conducted by the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary Group. Eighty-five patients were randomly assigned combined treatment (n = 42) or immunotherapy (n = 43) alone (controls). All patients had metastatic renal-cell carcinoma that had been histologically confirmed and was progressive at the time of entry. In study patients, surgery was done within 4

weeks of randomization and interferon (5×10^6 IU/m^2 subcutaneously 3 times per week) started 2-4 weeks later. In controls, interferon was started immediately after randomization.

Of the 42 assigned to the study group (surgery and immunotherapy), only 29 completed 16 weeks of immunotherapy. Six patients had perioperative complications that necessitated minor delays in the initiation of interferon treatments. Nevertheless, time to progression (5 vs 3 months, hazard ration of 0.60, 95% CI 0.36-0.97) and median duration of survival were significantly better in study patients than in controls (17 vs 7 months, 0.54, 0.31-0.94). Five patients responded completely to combined treatment, and 1 to interferon alone. Dose modification was necessary in 32% of patients, most commonly because of nonhematological side effects.

COMMENT BY WILLIAM B. ERSHLER, MD

These results clearly demonstrate an increased complete response (CR) rate and a survival benefit for those that receive combined nephrectomy and immunotherapy compared to immunotherapy alone. Why would such occur? One possible explanation is that a surgical debulking could result in spontaneous regression, as has been reported now and again.[5] However, the overall frequency has been calculated to be about 0.7%, which is actually less than operative mortality (1-5%). Nevertheless, previous nephrectomy may enhance response to systemic therapy, and the current data would support that contention.

Another reason to contemplate nephrectomy in patients presenting with metastatic disease relates to quality of life and reduction of morbidity. Removing the primary tumor would likely reduce tumor pain and hematuria, both of which can be a major cause of morbidity for renal cancer patients. Furthermore, the tumor wasting syndrome, felt to be paraneoplastic, at least in part, might be ameliorated after nephrectomy, although, in the presence of metastatic disease, this amelioration of systemic symptoms is likely to be of short duration.

This trial affords information regarding 2 critical questions with regard to nephrectomy for patients presenting with metastatic renal cancer: 1) do patients tolerate the procedure well enough to receive systemic therapy?; and, 2) does removal of the primary tumor increase the likelihood of an objective response to immunotherapy observed in the metastatic lesions? The data would indicate that both are true. However, the trial was relatively small and needs to be confirmed before such an approach becomes standard of care. In this regard, the findings from a similarly constructed SWOG trial (8949), will be very instructive. Early reports indicate a similar survival advantage has been observed for those receiving nephrectomy and immunotherapy.[6] ❖

References

1. Godley PA, Taylor M. *Curr Opin Oncol.* 2001;13: 199-203.
2. Scheltema JMW, Mickisch GH. *European Urology Update Series*. 1997;6:27-33.
3. Bukowski RM. *Semin Urol Oncol*. 2001;19:148-154.
4. O'Connell JR, et al. *Semin Urol Oncol*. 1996;23:1728.
5. Van Poppel H, Baert L. *Acta Urol Bélgica.* 1996;64: 11-17.
6. Flanigan RC, et al. *J Urol.* 2000;163(Suppl):685.

Is Circulating HER-2 a Prognostic Factor for Metastatic Breast Cancer Patients?

ABSTRACT & COMMENTARY

Synopsis: The prognostic and predictive significance of circulating levels of extracellular domain of HER-2 (ECD/HER-2) in patients with metastatic breast cancer was evaluated in 242 metastatic breast cancer patients. Elevated levels of ECD/HER-2 were present in 35-40% of patients and were associated with a poorer prognosis of these patients. However, elevated levels were not associated with resistance to endocrine therapy or with sensitivity to anthracycline-based chemotherapy. Additional study is needed to determine the clinical use of detecting circulating ECD/HER-2.

Source: Hayes DF, et al. *Clin Cancer Res*. 2001;7: 2703-2711.

Biologic markers have demonstrated use for treatment decision making for patients with metastatic breast cancer. The estrogen receptor (ER) and progesterone receptor (PR) status of breast cancers represent important biologic markers that influence decision making about endocrine-based therapies for these patients. Additional biologic markers could provide valuable tools for treatment decision making. A candidate marker for these patients is the c-erb B-2 gene and its protein products (also designated HER-2 and c-neu). The protein product of the HER-2 proto-oncogene is a 185-kd transmembrane glycoprotein with intracellular tyrosine kinase activity that is overex-

pressed in 20-40% of human breast cancers.[1] In addition, circulating levels of extracellular domain of HER-2 (ECD/HER-2) have been detected in blood and other body fluids of breast cancer patients.[2] Several studies have evaluated the potential role of HER-2 as a prognostic factor for breast cancer patients. While some conflicting results exist in the literature, available data suggest that overexpression or amplification of HER-2 is a weak to moderate-negative prognostic factor in the setting of primary breast cancer.[1] Several studies have suggested a weak to moderate-negative predictive ability of HER-2 regarding response to adjuvant endocrine therapy or to adjuvant alkylating agent therapy.[1] In addition, a moderate positive predictive value has been associated with HER-2 and response to adjuvant anthracycline-based therapy.[1] However, the HER-2 status of the tumor is not currently considered to be a sufficiently powerful factor upon which to base treatment decisions about overall adjuvant systemic therapy or adjuvant endocrine therapy.[1] Anthracyclines are suggested to be the preferred therapy when adjuvant chemotherapy is recommended.[1] For patients with metastatic disease, the HER-2 status is a strong predictive factor for response to trastuzumab.[1] Thus, monitoring circulating levels of ECD/HER-2 in patients with metastatic breast cancer have the potential to be a useful biologic marker for these patients.

This study by Hayes and associates is a laboratory monitoring study of 242 breast cancer patients entered into Cancer and Leukemia Group B (CALGB) prospective therapeutic trials for metastatic breast cancer. Eligible patients were entered into 1 of 8 therapeutic protocols involving endocrine therapy (1 of 3 doses of megestrol acetate [103 patients in 1 study]) or chemotherapy (139 patients receiving standard or investigational chemotherapy in 7 studies). Plasma samples were obtained for the ECD/HER-2 assay prior to treatment. Elevated baseline levels of ECD/HER-2 were detected in 89 of the 242 patients (37%). The elevated levels of ECD/HER-2 were significantly associated with PR levels (but not ER levels), number of prior treatments, and visceral metastases. Elevated initial ECD/HER-2 levels were univariately associated with shorter overall survival (OS). However, after adjusting for other clinical variables (number of prior treatments, primary treatment regimen, performance score, and tissue ER content), ECD/HER-2 levels were not independently correlated with OS. The median OS for patients on megestrol acetate with elevated pretreatment ECD/HER-2 was 20.2 months compared with 27.8 months for patients without elevated pretreatment ECD/HER-2 and was significant by univariate analysis ($P = 0.007$). However, this interaction did not reach a conventional level of significance following multivariate analysis to account for prior treatments, performance score, and tissue ER content ($P = 0.063$). There was no significant difference for overall survival, time to treatment progression, or response rates to chemotherapy between patients with elevated and without elevated pretreatment ECD/HER-2 levels. Hayes et al conclude that 40% of metastatic breast cancer patients have elevated circulating levels of ECD/HER-2, and elevated circulating levels of ECD/HER-2 were associated with worse survival. However, elevated levels of ECD/HER-2 were not associated with resistance to endocrine therapy or sensitivity to anthracycline-based therapy.

COMMENT BY MARK R. ALBERTINI, MD

Additional informative biomarkers would represent a welcome advance to help direct therapy for patients with metastatic breast cancer. The protein product of HER-2 is an attractive candidate for this role.[3] Tissue measurement of HER-2 is a strong predictive factor for response to trastuzumab, and a potential role for directing adjuvant therapies has been suggested.[1] Prospective randomized clinical trials will be needed to clarify the use of this marker for adjuvant treatment decisions. The current study addresses the issue of whether baseline levels of ECD/HER-2 will be useful to direct treatment decisions for patients with metastatic disease. Hayes et al successfully demonstrate the ability to obtain and analyze data for this marker within the context of cooperative group clinical trials. They also demonstrate and confirm detection of elevated levels of ECD/HER-2 in approximately 40% of patients with metastatic breast cancer. The association of a poorer prognosis with elevated baseline levels of ECD/HER-2 suggests a potential prognostic role for this marker. However, no ability to predict response to endocrine or chemotherapy interventions was demonstrated for this marker. Thus, the question remains as to whether circulating HER-2 is more than just a marker of tumor burden?[3]

Several aspects of this study merit consideration to determine the potential use of ECD/HER-2 to predict response of metastatic breast cancer patients to either hormonal or chemotherapeutic intervention. The only hormonal intervention in this study was megestrol acetate. Thus, responses to other hormonal interventions require further investigation. In addition, the patients receiving second-line megestrol acetate had already progressed on first-line hormonal therapy and could represent a selected group of patients with a poorer prognosis. The analysis of patients receiving anthracycline-based chemotherapy did not demonstrate an inter-

action between pretreatment ECD/HER-2 levels and sensitivity to chemotherapy. However, the HER-2 positive patients did equally well as the HER-2 negative patients even though the HER-2 status may have identified them as having a worse prognosis. Additional study with patients receiving uniform anthracycline and nonanthracycline therapy will be needed to best evaluate this question. The potential role of ECD/HER-2 to direct trastuzumab therapy merits investigation. In addition, the ability of sequential monitoring of ECD/HER-2 to demonstrate response to therapy or disease recurrence requires clinical testing. The evaluation of ECD/HER-2 as a biologic marker for patients with metastatic breast cancer is clinically feasible and merits additional investigation. ❖

References

1. Yamauchi H, et al. *J Clin Oncol.* 2001;19:2334-2356.
2. Hait WN. *Clin Cancer Res.* 2001;7:2703-2710.
3. Baselga J. *Clin Cancer Res.* 2001;7:2605-2607.

CME Questions

22. Which one of the following statements is *false* about ECD/HER-2 and patients with metastatic breast cancer?

a. ECD/HER-2 levels are elevated in 35-40% of patients with metastatic breast cancer.
b. Elevated levels of ECD/HER-2 are associated with a poorer prognosis for patients with metastatic breast cancer.
c. Pretreatment levels of ECD/HER-2 can be used to predict response to hormonal and chemotherapy treatments for patients with metastatic breast cancer.
d. Pretreatment levels of ECD/HER-2 can be determined within the context of a cooperative group clinical trial.

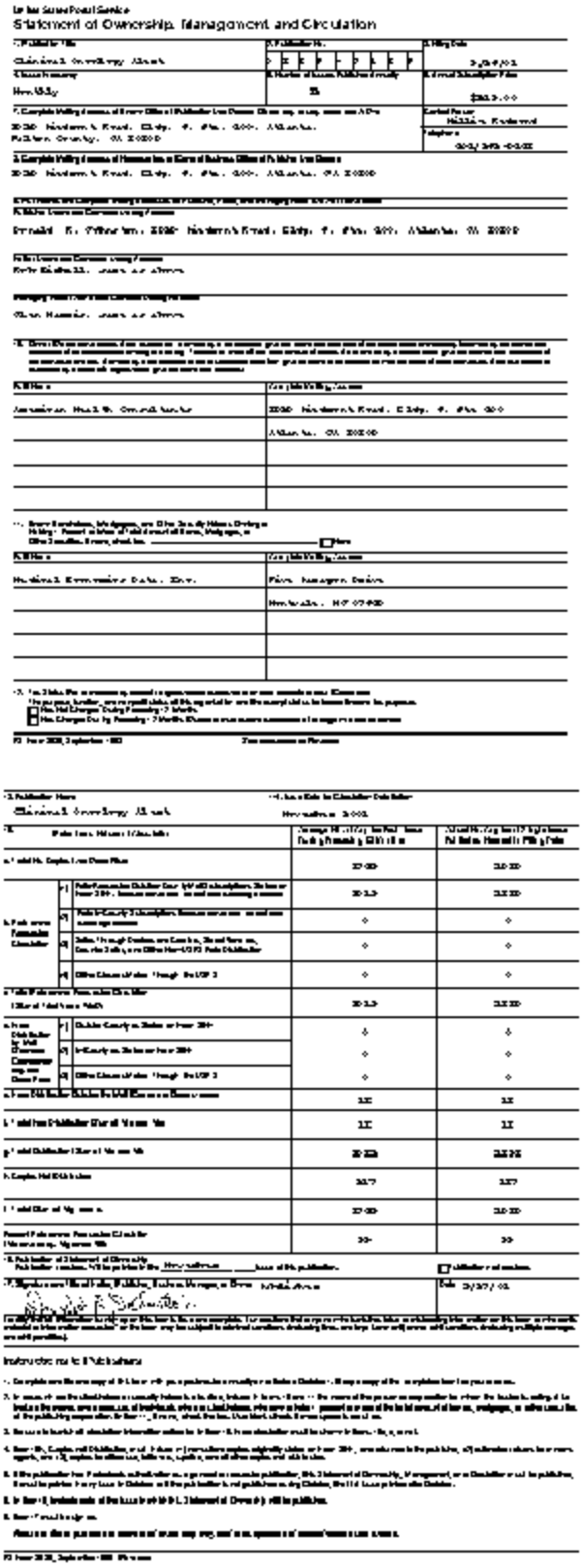
23. Published interim data from phase III trials support a survival benefit with use of radiochemotherapy for patients with:

a. adenocarcinoma of the esophagus.
b. squamous cell carcinoma of the esophagus.
c. Both
d. Neither

24. In the Shanghavi trial, they declared that stereotactic radiosurgery:

a. offered the largest benefit to patients with metastatic malignant melanoma.
b. should be performed prior to whole brain radiotherapy in order to be most effective.
c. is comparable to surgical resection with respect to local control of solitary brain metastases.
d. prolonged overall survival in all prognostic classes.

Annual Statement of Ownership, Management, and Circulation


Statement of Ownership, Management, and Circulation

In Future Issues:

Rituxan and CLL