AMERICAN HEALTH CONSULTANTS®

Providing Evidence-based Clinical Information for 18 Years

CLINICAL ONCOLOGY ALERT

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

Cancer Treatment in the Oldest-Old: Evidence for an Age Bias Against the Use of Tamoxifen

ABSTRACT & COMMENTARY

Synopsis: *Breast cancer occurs with increasing frequency throughout the lifespan, and there is mounting evidence that when it occurs in the oldest-old (those older than 85 years of age), less cancer-directed treatment is provided. In this report, tamoxifen use was compared in patients 80-84 years and 85-92 years. The results indicate that there was a greater than 25% drop-off in tamoxifen prescriptions between the 2 groups. Doctors tend to prescribe less tamoxifen to the oldest-old and also to those with significant comorbidities (in both age groups) or those unmarried and without living children. With increasing life expectancy currently being observed in these age groups, this study raises the possibility that oncologists may be missing the opportunity to help the oldest breast cancer patients achieve therapeutic benefit from tamoxifen.*

Source: Blackman SB, et al. *Cancer*. 2002;95:2465-2472.

Adjuvant tamoxifen is currently recommended for estrogen receptor-positive breast cancer, regardless of patient age. Although there is quite substantial evidence that older patients are less likely to be treated with cytotoxic chemotherapy, little data exist with regard to tamoxifen treatment, particularly in those patients older than 80 years of age. Blackman and colleagues studied 92 patients diagnosed at 4 US sites with primary, early stage breast cancer by phone interview (on 2 occasions) and medical record review. They compared the proportion of patients treated with tamoxifen in the 80-84 age group with those aged 85-92 years.

Before adjustment for comorbidities, patients aged 85-92 years were 28% less likely to receive a tamoxifen prescription compared with patients 80-84 years of age (relative risk [RR] = 0.72; 95% confidence interval [CI], 0.57-0.91). In this sample, patients not prescribed tamoxifen had substantially more comorbidity, but even after adjusting for comorbidity, the RR was 0.74 (95% CI, 0.58-0.93). In addition, the oldest patients and those not treated with tamoxifen were significantly less likely to be married or have living children.

VOLUME 18 • NUMBER 3 • MARCH 2003 • PAGES 17-24

INSIDE

The data from this review indicate a reduction in the use of tamoxifen in the oldest age group of breast cancer patients. Blackman et al speculate that given the increasing longevity of the oldest-old, undertreatment with adjuvant tamoxifen may put older breast cancer patients at an increased risk of disease recurrence and breast cancer mortality.

COMMENT BY WILLIAM B. ERSHLER, MD

This study has some important limitations, primarily based upon its rather small size and the likely possibility that those agreeing to be included and proceeding through the 2 interviews might not be truly representative of the population of interest (the oldest subset of breast cancer patients). Nonetheless, to my knowledge, this is the first report examining tamoxifen use in the oldest-old, and the findings support the notion that patients in this age group may be undertreated.

Breast cancer occurs with increasing numbers with each advancing decade. For example, compared with women 50-54 years of age, women 80-84 years of age have a 1.8-fold greater incidence of breast cancer and a 3.2-fold greater likelihood of dying of this disease.[1] Currently, women 80 years and older account for 13% of new breast cancer cases but 27% of breast cancer deaths[2] and the absolute numbers will increase dramatically in the next few decades as this age group is the fastest growing of all aging subsets in the United States.

One reason the death rate is higher for older women may relate to the less aggressive treatment they receive, when compared to younger women.[3,4] For example, women older than 80 years are about 3 times less likely to receive guideline primary tumor therapy by not receiving radiation therapy following breast conserving surgery (BCS), compared with women 67-79 years of age.[5] Additionally, breast cancer patients with poor family support, including unmarried patients without living children, are at a greater risk of receiving less than guideline primary surgical therapies and have poorer survival outcomes when compared to married patients who have living children.[6,7]

One possible explanation for the reduced tamoxifen use in the oldest breast cancer patients is a perception by treating oncologists that the toxicity might be greater in this age group or that a limited life expectancy due to the patient's advanced age minimizes the chance for realizing therapeutic benefit. However, there is no solid evidence that tamoxifen toxicity is greater in the elderly. In fact, vasomotor symptoms, such as night sweats and hot flashes, have been reported to decrease with age.[8]

With regard to limited life expectancy, it should be recalled that the average expectancy at age 85 is 9.6 years, and at age 90, life expectancy is 6.8 years. Thus, patients with early breast cancer may well have time to achieve a meaningful benefit from tamoxifen treatment. ■

References

1. Ries L, et al. Seer Cancer Statistics Review 1973-1988. http://seer.cancer.gov/publications/CSR1973_1988/2001.
2. American Cancer Society. Breast cancer facts and figures 2001-2002. http://www.cancer.org.downloads/STT/BrCaFF2001.
3. Silliman RA, et al. *Cancer*. 1997;80:1326-1334.
4. Hebert-Croteau N, et al. *Cancer*. 1999;l85:1104-1103.
5. Mandelblatt JS, et al. *Cancer*. 2000;89:561-573.
6. Neale AV, et al. *Soc Sci Med*. 1986;23:305-312.
7. Goodwin JS, et al. *JAMA*. 1987;258:3125-3130.
8. Powles T, et al. *Lancet*. 1998;352:98-101.
9. National Center for Health Statistics. http://www.cdc.gov/nchs/datawh/statab/unpubd/mortabs/lewk3.htm.

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: Brenda Mooney.
EDITORIAL GROUP HEAD: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
MANAGING EDITOR: Robin Mason.
ASSISTANT MANAGING EDITOR: Robert Kimball.
SENIOR COPY EDITOR: Christie Messina.

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: $38.
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.

THOMSON
AMERICAN HEALTH CONSULTANTS

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
1 year *with* free AMA Category 1 credits: $279
(Student/Resident rate: $140).

Multiple Copies
1-9 additional copies: $206 each; 10 or more copies: $183 each.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the 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.

Questions & Comments

Please call **Robin Mason,** Managing Editor, at (404) 262-5517 or **Robert Kimball,** Assistant Managing 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.

Omission of Chemoradiation is Associated with Poor Survival in Medicare Patients with Resected Pancreas Cancer

ABSTRACT & COMMENTARY

Synopsis: *Outcomes following resection of pancreas cancer have improved recently, more than can be accounted for by a drop in procedure-related mortality. This study from the Harvard School of Public Health performed a retrospective analysis of claims-based Medicare data and correlated it with SEER data to identify prognostic factors that may be contributing to this phenomenon.*

Source: Lim JE, et al. *Ann Surgery*. 2003;237:74-85.

The NCI SEER program collects demographic and tumor registry data, including surgery and radiotherapy information, for areas of the country reflecting approximately 14% of the US population. Chemotherapy data are considered unreliable because outpatient chemotherapy can be missed. Lim and colleagues from Harvard Medical School performed a retrospective cohort study on patients treated from 1991-1996 by merging SEER files with Medicare claims data in order to identify potential prognostic factors related to postresection survival in patients with pancreas cancer. Using ICD-9 and DRG codes, Lim et al correlated inpatient and outpatient files with physician and lab billing data from the Health Care Finance Administration (HCFA) database and identified 6 prognostic factors that were significantly related to survival in a multivariate analysis.

Medicare enrollees residing in 1 of the 11 SEER catchment areas who were treated surgically with curative intent were included in the study. HMO patients were excluded because of incomplete reporting to HCFA during the study period. Curative resections were either radical pancreaticoduodenectomy or a Whipple procedure. A total of 396 patients were identified, with a median age of 72 years. There were 196 women and 200 men. Connecticut contributed the most patients. There were 321 Caucasians, 29 African Americans, 20 Asians, and 26 unspecified. Among the patients studied, 185 (46.7%) received some form of adjuvant therapy, including 125 who received adjuvant chemoradiation, 49 who received RT alone, and 11 who received chemotherapy alone. Further details regarding adjuvant therapy doses and schedules were not provided. Patients who received adjuvant therapy were slightly younger (71.3 vs 73.3 years) and were more likely to have above-median income (59% vs 48%) than patients who were treated with surgery alone. They were also more likely to have had lymph nodal involvement. Factors assessed included: demographic details like age, gender, race, ethnicity, and socioeconomic status; perioperative issues such as type of resection (partial, etc), transfusions, teaching venue, and adjuvant therapy; and histopathologic findings such as tumor size, tumor grade, and TNM stage.

Median follow-up was 38.5 months (range, 0.2-44.8). Median tumor diameter was 3 cm. No regional variation in assignment of adjuvant treatment was identified, and the use of adjuvant therapies did not change over the course of the study period. More patients were resected in teaching facilities as the study period progressed, including 64% of all the patients. Median overall survival for the entire group was 17.6 months. One-year survival was 60.1% and 3-year survival was 34.3%. There was a statistically significant difference in median survival for those patients who received adjuvant therapy compared with those who did not. Post-chemoradiation median survival was 29 months compared with 12.5 months for no adjuvant treatment, 1-year survival was 81% vs 51%, and 3-year survival was 45% vs 30% ($P = 0.0003$).

Multivariate analysis revealed no significant difference in outcome based on Whipple vs non-Whipple resection, number of units transfused, or T-stage. Six variables were shown to be statistically significantly related to survival, including absence of adjuvant therapy ($P = .0002$), tumor diameter > 2 cm ($P = .004$), positive lymph nodes ($P = .009$), Grade 2 or 3 ($P = .01$), nonteaching venue ($P = .01$), and low SES ($P = .02$). Patients with 1-3 positive lymph nodes did as well as patients with negative lymph nodes.

Lim et al concluded that their findings were consistent with those of the Gastrointestinal Study Group randomized trial results published in 1985,[1] but cautioned that certain aspects of their study may limit the accuracy of their conclusions. For example, 27% of patients with pancreas cancer are younger than 65 years, and were excluded from the study population. There was no assessment of surgical margin status, ploidy, or lymphvascular invasion, and there was no central pathology review. The advantage seen with surgery in a teaching center may have been a proxy for high-volume hospitals. The findings relating to SES may have reflected access

to care issues, or possibly patient preference. While the most significant predictor of survival following resection was the administration of adjuvant therapy, further studies are needed to confirm these observations.

COMMENT BY EDWARD J. KAPLAN, MD

This study is interesting because it involved a reasonably large number of patients and covered a wide geographic area. The method used by Lim et al was innovative. Their conclusions were not surprising, except that the patients who received adjuvant therapy were more likely to be node positive, but still did better than those who received surgery alone. In their paper, Lim et al made reference to the 2 recently completed European randomized trials that looked at the effect of adjuvant chemoradiation on outcomes in resected pancreas cancer. The EORTC 40891 trial accrued patients from 1987-1995 and included 114 evaluable patients with pancreas cancer. This trial randomized between surgery alone vs surgery followed by 40 Gy split-course RT and 5-FU. Preliminary results were published in 1999 and showed no significant benefit with adjuvant chemoradiation.[2] However, given the poor track record for split- course RT, the small sample size, and the fact that 20% of the patients assigned to adjuvant chemoradiation did not receive it, the early results of the EORTC trial are not convincing. The second trial cited was the ESPAC-1 trial from the European Study Group for Pancreatic Cancer. This trial ran from 1994-2000 and enrolled 541 patients. It randomized patients between adjuvant 5-FU vs 20 Gy + 5-FU vs observation and found no survival benefit for adjuvant chemoradiotherapy. According to the first published results from Neoptolemos, each of the 61 cancer centers relied on its own RT quality assurance standards to deliver the radiotherapy according to local practice. They concluded that the ESPAC-1 results "clear the way for focusing on chemotherapy as the principle adjuvant modality in pancreatic cancer . . . " Not surprisingly, an ASCO abstract from 2002 combining the GITSG, EORTC, and ESPAC-1 data along with data from a Norwegian trial into a meta-analysis likewise concluded that chemoradiation offered no survival benefit.[4]

I have to differ with the statement made in the ESPAC-1 report. I think their results clear the way for the RTOG 9704 randomized trial results, since it is the only modern randomized trial that used RT doses that would be considered efficacious (ie, 50.4 Gy with concomitant radiosensitizing 5-FU vs gemcitabine). This trial closed recently and was omitted in the discussion by Lim et al. I would tend to give much greater credence to its results than I would to those from the 2 European trials, both of which I consider to have been woefully deficient from a radiotherapy perspective.

References

1. GITSG. *Arch Surg*. 1985;120:899-903.
2. Klinkenbijl JH, et al. *Ann Surg*. 1999;230:776-784.
3. Neoptolemus JP, et al. *Lancet*. 2001;358:1576-1585.
4. Dunn JA, et al. *Proc ASCO*. 2002;abstract 564.

Lung Cancer in Asian Immigrants: More-Advanced Disease, Less-Favorable Outcomes

ABSTRACT & COMMENTARY

Synopsis: *In a 5-year retrospective analysis of lung cancer in Asian immigrants living in Boston and seen at the New England Medical Center, more-advanced disease and shorter survival was observed when compared to non-Asian, and age- and gender-matched controls.*

Source: Finlay GA, et al. *Chest*. 2002;122:1938-1943.

In Boston, like many urban locations throughout the United States, there has been a fairly dramatic increase in the Asian population. To test a clinical hypothesis that Asian immigrants presented with more-advanced disease and had shorter lung cancer survival, Finlay and colleagues at New England Medical Center performed a 5-year retrospective case-control study (1992-1996) in which 42 Asian immigrants with lung cancer diagnosed over the study period were matched for age and sex with 42 non-Asian control subjects. The Asians presented more frequently with advanced stage (stage III or IV) disease and less frequently with early stage disease (stage I or II) than the non-Asian control group ($P < 0.05$). Asians were also more likely to present with hemoptysis or constitutional symptoms ($P < 0.01$) and had a longer duration of symptoms prior to presentation ($P < 0.01$). The incidence of large-cell carcinoma was higher in Asians ($P < 0.05$). Diagnostic procedures and length of time from diagnosis to treatment were not significantly different. The treatment of stage I and II disease did not differ, but for the more advanced stages,

Asians were more likely to receive radiation therapy alone and not combination therapy, compared to non-Asian controls ($P < 0.05$). The median 2-year survival was significantly reduced in Asians (7 months) compared with non-Asians (15 months) ($P < 0.001$). Thus, in this retrospective review, the clinical hypothesis that Asian immigrants present with more advanced disease and have shorter survival was proven true.

COMMENT BY WILLIAM B. ERSHLER, MD

It is impossible to tell from the current report whether there is an inherently more aggressive nature of lung cancer in Asian immigrants, although this might be discernible in a larger study, from which survival in stage-matched patients could be assessed. However, the increased number with large-cell histology would suggest that certain genetic or environmental factors may explain some of the differences observed in the Asian patients. Certainly, social factors may be of equal or even greater importance in explaining the findings. For any of a number of reasons, the Asian patients included in this survey delayed seeking medical attention (ie, had symptoms for a longer time), and at the time of diagnosis were found to have more advanced disease. Fewer presented with early stage disease and, not surprisingly, survival was shorter.

The data presented were not dissimilar from what has been observed with African Americans[1-3] demonstrating more advanced disease at presentation, fewer curative resections, and shorter survival.

Social factors that may be involved in the delay in diagnosis include language barriers, a reluctance to be treated with Western medicine, or a lack of financial resources to gain access to care. Certainly, other factors are involved as well. Whatever the explanation, clinicians need to be aware that lung cancer in Asian immigrants will become increasingly apparent with our changing demography, particularly in urban populations, and the persistent use of cigarettes throughout this culture. Furthermore, we need to be especially vigilant in light of the fact that such patients present with more advanced disease. It is likely that for the near future, our best chance for influencing this unfavorable picture would be a community-based educational program that would encourage smoking cessation and earlier diagnostic interventions. ■

References

1. Landis S, et al. C*A Cancer J Clin*. 1998;48:6-29.
2. Greenwald HP, et al. *Am J Public Health*. 1998;88:1681-1684.
3. Bach PB, et al. *N Engl J Med*. 1999;341:1198-1205.

CHOP and Non-Hodgkin's Lymphoma

ABSTRACTS & COMMENTARY

Synopsis: *CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is still considered the gold standard in first-line therapy for aggressive non-Hodgkin's lymphoma. Despite its place in clinical practice for 3 decades, there are issues that still are being evaluated. The February 2003 issue of the* Annals of Oncology *reports on the issue of cardiotoxicity of CHOP, and a second article discussed the use of a modified CHOP regimen in patients older than 65.*

Sources: Limat S, et al. *Ann Oncol*. 2003;14:277-281; Bessel EM, et al. *Ann Oncol*. 2003;14:258-267.

Anthracyclines are a main component for the treatment of various solid tumors and hematologic malignancies. They have a known spectrum of toxicity, particularly cardiac toxicity. Cardiotoxicity is increased in the elderly and pediatric patients.[1] Cardiac function is monitored during therapy and as follow-up through the MUGA (multiple-gated acquisition) scan. Monitoring can detect changes in left ventricular function but may not decrease the incidence of cardiomyopathy due to its inability to predict toxicity. In order to minimize lifetime risk of cardiotoxicity, it is recommended to limit cumulative doxorubicin doses to 550 mg/m^2 and daunorubicin doses to 500 mg/m^2 in adults. The cumulative incidence of congestive heart failure varies from 1.6% to 2.8%. Depending on the sensitivity of the measure, cardiac abnormalities can be seen in up to 57% of long-term survivors. Dexrazoxane (Zinecard®) is a cardioprotectant for patients receiving doxorubicin that decreases the incidence of cardiotoxicity with therapy above recommended dosage limits in breast cancer.[2-4]

COMMENT BY STUART M. LICHTMAN, MD, FACP

Limat and colleagues carried out a retrospective study to analyze the early doxorubicin-induced cardiotoxicity in aggressive NHL patients. The primary objective was to determine the incidence of cardiac abnormalities within 1 year of treatment with the CHOP regimen. The secondary objective was to identify risk factors. Cardiac events were defined as either a decline in resting LVEF of 15% from baseline, or a decline in LVEF of < 50%, or clinical evidence of CHF. Twenty-seven patients (20%) developed a cardiac event within 1

year of treatment. Among these, 14 patients had clinical signs of CHF. Three patients died suddenly from presumed cardiac causes. An analysis showed a cumulative dose of doxorubicin > 200 mg/m^2 and age older than 50 years appeared to be significant risk factors. These were unselected patients who had previously not had chemotherapy or radiation therapy. The use of more sensitive investigators has led to a wider definition of cardiotoxicity, including subclinical cardiomyopathy. The evaluation of diastolic dysfunction and serum troponin-T levels needs to be further evaluated as diagnostic or predictive tools. Preventive strategies to decrease toxicity can include prolonged infusions, potentially less cardiotoxic drugs (ie, epirubicin, mitoxantrone), and liposomal compounds. These alterations in treatment programs including the use of dexrazoxane need to be evaluated in prospective trials.

Studies should include those patients who potentially are at increased risk such as the elderly, patients with prior heart disease, and patients with prior or concomitant chest irradiation.[5,6]

Bessel and colleagues conducted a study to determine whether there was a difference in toxicity between modified CHOP and MCOP chemotherapy in elderly patients (median, 74 years; range, 65-91). CHOP was modified by lowering the dose of cyclophosphamide to 600 mg/m^2 and doxorubicin to 30 mg/m^2. MCOP substituted mitoxantrone 10 mg/m^2 for doxorubicin.

The treatment of elderly patients with lymphoma has been studied with a number of different regimens trying to improve on standard CHOP. To date, CHOP remains the standard of care. More recently, the addition of rituxamib has been shown to improve outcome.[7] The complete response rate in the current study was CHOP 62% and MCOP 52% (NS; P = .26). The only significant difference in toxicity was in red cell transfusion and white cell counts. There were no sufficient data to determine whether there was any difference in cardiac toxicity. There was no significant difference in overall survival.

The International Prognostic Index indicates that age older than 60 years is an adverse prognostic factor.[8] Due to poor survival and decreased tolerance to standard chemotherapy, a number of trials have tried to improve on the standard CHOP regimen for elderly patients.[9] This has included weekly therapy, substitution of mitoxantrone for doxorubicin, and elimination of the anthracycline.[10-12] These modifications have led to less-effective regimens. The current study and those cited do not include the supportive care measures that are now commonly employed. Newer antiemetic regimens and hematopoietic growth factors were often not included. This certainly can ameliorate some of the toxicities seen in these studies. In addition, the current study also demonstrated that in lymphoma trials in elderly patients, many deaths on study are not due to lymphoma or toxicity.[13] In this trial, 26% of patients died from other causes. Therefore, cause of death, comorbidity and other functional factors need to be assessed to determined the overall efficacy of a particular regimen. ■

References

1. Singal PK, Iliskovic N. *N Engl J Med*. 1998;339: 900-905.
2. Swain SM, et al. *J Clin Oncol*. 1997;15:1318-1332.
3. Doroshow JH. Anthracyclines and anthracenediones. In: Chabner BA, Longo DL, eds. *Cancer Chemotherapy and Biotherapy: Principles and Practice*. 2nd ed. Philadelphia: Lippincott-Raven; 1996:409-434.
4. Doroshow JH. *N Engl J Med*. 1991;324:843-845.
5. Von Hoff DD, et al. *Ann Intern Med*.1979;91:710-717.
6. Ibrahim NK, et al. *Ann Oncol*. 2000;11:1597-1601.
7. Coiffier B, et al. *N Engl J Med*. 2002;346:235-242.
8. *N Engl J Med*. 1993;329:987-994.
9. Lichtman SM. *Crit Rev Oncol Hematol*. 2000;33: 119-128.
10. Meyer RM, et al. *J Clin Oncol*. 1995;13:2386-2393.
11. Sonneveld P, et al. *J Clin Oncol*. 1995;13:2530-2539.
12. Bastion Y, et al. J *Clin Oncol*. 1997;15:2945-2953.
13. Vose JM, et al. *J Clin Oncol*. 1988;6:1838-1844.

Anti-HER2 Antibody, Trastuzumab in Patients with Recurrent or Refractory Ovarian or Primary Peritoneal Carcinoma with Overexpression of HER2

ABSTRACT & COMMENTARY

Synopsis: *The clinical value of single-agent trastuzumab in recurrent ovarian cancer is limited by the low frequency of HER2 overexpression and low rate of objective response among patients with HER2 overexpression.*

Source: Bookman MA, et al. *J Clin Oncol.* 2003;21: 283-290.

In a phase II clinical trial of the gynecologic Oncology Group (GOG), Bookman and colleagues

evaluated the feasibility, toxicity, and efficacy of single-agent monoclonal antibody therapy targeting the human epidermal growth factor receptor 2 (HER2)/neu receptor in ovarian and primary peritoneal cancer. Eligible patients had measurable persistent or recurrent epithelial ovarian or primary peritoneal carcinoma with 2+ or 3+ HER2 overexpression documented by immunohistochemistry. Intravenous trastuzumab was administered initially at a dose of 4 mg/kg, then weekly at 2 mg/kg. Patients without progressive disease or excessive toxicity could continue treatment indefinitely. Those with stable or responding disease at 8 weeks were offered treatment at a higher weekly dose (4 mg/kg) at time of progression. Patient sera were analyzed for the presence of the soluble extracellular domain of HER2, host antibodies against trastuzumab, and trastuzumab pharmacokinetics. A total of 837 tumor samples were screened for HER2 expression, and 95 patients (11.4%) exhibited the requisite 2+/3+ expression level. Forty-five patients, all of whom received prior chemotherapy, were entered, and 41 were deemed eligible and assessable. There were only mild expected toxicities and no treatment-related deaths. Although an elevated level of the soluble extracellular domain of HER2 was detected in 8 of 24 patients, serum HER2 was not associated with clinical outcome. There was no evidence of host antitrastuzumab antibody formation. Serum concentrations of trastuzumab gradually increased with continued therapy. An overall response rate of 7.3% included 1 complete and 2 partial responses. Median treatment duration was 8 weeks (range, 2-104 weeks), and median progression-free interval was 2.0 months. Bookman et al concluded that the clinical value of single-agent trastuzumab in recurrent ovarian cancer is limited by the low frequency of HER2 overexpression and low rate of objective response among patients with HER2 overexpression.

COMMENT BY DAVID M. GERSHENSON, MD

Over the past few years, with the completion of the Human Genome Project and the explosion of knowledge in the field of cancer biology, targeted therapeutics is foremost in the minds of both patients and oncologists. While chemotherapy is very much a "shotgun" approach, the hope for targeted therapy is that one will be able to eventually individualize therapy based on the molecular profile of each patient's tumor. Although we are not currently near that goal, several potential targets involved in tumorigenesis have been identified. These include growth factors, oncogenes, tumor suppressor genes, and angiogenic/vascular factors. The HER-2/neu oncogene is one of the prime candidates. Abnormal expression of HER-2/neu has been reported in a number of cancers, including ovarian cancer. Initial studies suggested that approximately 30% of ovarian cancers overexpress the HER-2/neu oncogene. However, this study and several others, including our own experience, peg the overexpression rate at about 10% based on immunostaining. Therefore, HER-2/neu may not be such an attractive target for the majority of ovarian cancer patients. Furthermore, as a single agent, the monoclonal antibody to HER-2/neu had limited activity in patients with HER-2/neu overexpressing, refractory ovarian or peritoneal cancers, with a response rate of only 7.3%. This response rate is lower than the 12-15% response rate reported with trastuzumab in the treatment of metastatic breast cancer. Additionally, combinations of the monoclonal antibody plus chemotherapy have been reported to achieve response rates exceeding those for the single agents. Therefore, we may see additional studies with this agent in combination with chemotherapy for ovarian cancer patients. As Bookman et al point out, however, the low frequency of HER-2/neu overexpression may make such trials impractical. ■

Dr. Gershenson is Professor and Chairman, Department of Gynecology, M.D. Anderson Cancer Center, Houston, Tex.

CME Questions

8. Current evidence now indicates that physicians are less inclined to prescribe tamoxifen for the adjuvant treatment of breast cancer for which of the following subgroups of patients?

a. Those 85 years of age and older, compared to those 80-84 years old
b. Those who are currently unmarried (never married, divorced, or widowed) and without living children
c. Those who have 2 or more comorbid conditions
d. All of the above

9. In the Lim pancreas adjuvant therapy paper:

a. HMO data were combined with Medicare data to derive conclusions regarding potential prognostic factors.
b. SEER data were combined with patient interviews to derive conclusions regarding potential prognostic factors.
c. Medicare and SEER data were merged to derive conclusions regarding potential prognostic factors.
d. GITSG, EORTC, and ESPAC-1 data were combined to derive conclusions regarding potential prognostic factors.

10. Regarding the Lim pancreas cancer paper, which statement is correct?

a. The Lim, EORTC, and ESPAC-1 findings concurred regarding the efficacy of adjuvant chemoradiation.
b. The RTOG, EORTC, and ESPAC-1 findings were at odds with Lim et al's findings.

c. The Lim and RTOG findings were at odds with the EORTC and ESPAC-1 findings.
d. The Lim paper's conclusions were starkly different from those of the EORTC and ESPAC-1 randomized trial reports.

11. Lung cancer in Asian immigrants is:
a. more likely to present as stage I or stage II disease, when compared with non-Asian patients.
b. more likely to with asymptomatic disease (ie, be found on routine X-ray for unrelated indications) when compared with non-Asian patients.
c. more likely to present with hemoptysis and constitutional symptoms when compared with non-Asian patients.
d. more likely to be squamous cell histology, when compared with non-Asian patients.

Answers: 8 (d); 9 (c); 10 (d); 11 (c)

In Future Issues:

The Latest on Ovarian Adjuvant Therapy