AMERICAN HEALTH CONSULTANTS

CLINICAL ONCOLOGY ALERT

Providing Evidence-based Clinical Information for 17 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

Phase II Trial of Thalidomide in Renal-Cell Carcinoma

ABSTRACT & COMMENTARY

Synopsis: A phase II study is reported in patients with metastatic renal cell carcinoma using thalidomide. Patients were given doses up to 1200 mg if tolerable. A 5% objective response was observed with substantial toxicity. The true value of thalidomide in renal cell carcinoma has yet to be determined.

Source: Escudier B, et al. *Ann Oncol*. 2002;13:1029-1035.

Angiogenesis has been recognized as a key factor in tumor progression and has become a target for anti-neoplastic drug development.[1] Thalidomide, initially prescribed as a sedative and to ameliorate nausea in pregnancy in the 1950s, is known to have significant anti-angiogenic activity. Thalidomide demonstrated a capacity to eradicate experimental tumors in mice, to induce apoptosis of neovasculature established in experimental models, and to treat the vascular tumor, Kaposi's sarcoma. Thalidomide has been shown to be active in the treatment of lepromatous leprosy and other dermatologic disorders such as cutaneous lupus erythematosus, recurrent erythema multiforme, prurigo nodularis, and aphthous ulcers. Recently, activity has been shown in inflammatory and autoimmune diseases such as Bechet's syndrome, inflammatory bowel diseases, rheumatoid arthritis, sarcoidosis, and graft-versus-host disease. Thalidomide has also had activity in the treatment of chemoresistant multiple myeloma and gliomas.[2,3]

An investigation of thalidomide in renal cell carcinoma has been reported. Metastatic renal cell carcinoma is refractory to chemotherapy and median survival has been reported to range from 2-12 months. Both alpha-interferon and interleukin-2 have demonstrated some activity, both alone or combined, with objective response rates ranging from 5-40%. Forty patients were enrolled in the currently reported study. Eligibility included histologically confirmed metastatic renal cell carcinoma, an ECOG performance status 0-2, and adequate organ function. Thalidomide was administered nightly at 400 mg. The dose was increased to 800 mg after 6 weeks if disease was overtly progressive or after 12 weeks in the absence of an objective response. In patients whose disease continued to progress

Volume 17 • Number 9 • September 2002 • Pages 65-72

INSIDE

after 6 or 12 weeks at 800 mg, the dose was increased to 1200 mg if tolerated. The median age of the patients was 61 years and 80% had undergone nephrectomy. All but 6 had previously received immunotherapy.

The results were that no objective responses were observed at 12 weeks, but disease was stable in 11 patients. At 6 months, 2 patients achieved a partial response, corresponding to an overall response of 5%. These responses lasted 3 and 5 months. The 1-year survival rate was 38% and the median survival time was 10 months. Toxicity was significant, with fatigue and lethargy the most common. The fatigue score increased with time on therapy. Neurologic toxicity was substantial. Peripheral neuropathy was very common, with moderate at 20% and severe 15%. Thromboembolism was another significant toxicity. Nine patients had events during the first 12 weeks; 6 with deep venous thrombosis in the leg and 3 patients with vena cava thrombosis. Three patients also subsequently developed pulmonary embolism.

COMMENT BY STUART M. LICHTMAN, MD

Metastatic renal cell carcinoma continues to be an extraordinarily difficult problem in medical oncology. There are no standard therapies for the majority of patients with this disorder. Many patients are older and cannot tolerate therapy with high doses of interleukin-2. It was hoped that a less toxic, oral therapy such as thalidomide could provide some palliation for these patients. Unfortunately this is at least the second trial showing minimal to no clinical activity in this disease.[4] The results in this study demonstrate that despite giving patients doses upwards of 1200 mg, no benefit was observed. Even more concerning was the substantial toxicity observed. This clearly negates any potential palliative benefit of stable disease. Because stable disease can occur as part of the natural history of metastatic renal cell carcinoma, any potential benefit of disease stabilization would need to be addressed in a randomized trial. It should also be noted that severe, unexpected toxicity resulted when thalidomide was combined with alpha-interferon.[5]

Thalidomide has a number of potential clinical applications. Some of these were mentioned previously. The drug has shown clear benefit in patients with multiple myeloma relapsing after transplant. Activity has also been demonstrated in glioma and the suggestion of some benefit in hepatocellular carcinoma. Thalidomide has been shown to ameliorate the toxicity of irinotecan in the treatment of metastatic colorectal carcinoma. Studies are ongoing to determine whether thalidomide can reverse the wasting syndrome associated with HIV infection.[6]

This and other studies have failed to demonstrate significant benefit of thalidomide in renal cell carcinoma and have been associated with substantial toxicity at the doses used in this trial. Despite the wide availability of the drug, patients should be encouraged to enroll on clinical trials to determine the true value of this medication in both the treatment of solid tumors and nonmalignant disorders. ■

Dr. Lichtman is Associate Professor of Medicine, NYU School of Medicine, Don Monti Division of Medical Oncology, North Shore University Hospital, Manhasset, NY.

References

1. Escudier B, et al. *Ann Oncol*. 2002;13:1029-1035.
2. Singhal S, et al. *N Engl J Med*. 1999;341:1565-1571.
3. Fine HA, et al. *J Clin Oncol*. 2000;18:708-715.
4. Motzer RJ, et al. *J Clin Oncol*. 2002;20:302-306.
5. Nathan PD, et al. *J Clin Oncol*. 2002;20:1429-1430
6. Baidas S, et al. *Cancer Invest*. 2002;20:835-848.

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.
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 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.

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.

Salpingo-Oophorectomy Reduces Cancer Risk for Women with BRCA Mutations

ABSTRACTS & COMMENTARY

Synopsis: In a recent issue of the New England Journal of Medicine, 2 important studies addressing the role of prophylactic oophorectomy in individuals with BRCA mutations were published. The first was a nonrandomized, single institution (Memorial Sloan Kettering) prospective evaluation and the second was a multigroup (Prevention and Observation of Surgical End Points Study Group) retrospective analysis. The studies came to nearly identical conclusions; prophylactic oophorectomy reduces the occurrence of ovarian and breast cancer in women with BRCA mutations.

Sources: Kauff ND, et al. *N Engl J Med*. 2002;346: 1609-1615; Rebbeck TR, et al. *N Engl J Med*. 2002;346: 1616-1622.

Recently, the *New England Journal of Medicine* published 2 consecutive reports that provide solid evidence supporting the recommendation for bilateral salpingo-oophorectomy (BSO) for women who carry mutations in either BRCA1 or BRCA2 genes. The first was a prospective study from Memorial Sloan Kettering Cancer Center, in which Kauff and colleagues prospectively compared the risk-reducing effect of BSO with that of surveillance for ovarian cancer on the incidence of subsequent breast cancer. Women (n = 170) with either BRCA1 or BRCA2 chose to undergo either surveillance for ovarian cancer or risk-reducing salpingo-oophorectomy. At the time of this report the mean follow-up was 24.2 months. Three women from the group that had chosen prophylactic salpingo-oophorectomy were found to have early stage ovarian cancer at time of surgery and, during the follow-up period, one developed a primary peritoneal papillary serous carcinoma. Ovarian cancer developed in 5 of 72 women who elected to intensive surveillance rather than surgery. Several in both groups had previously undergone prophylactic mastectomy. Among women who had not had prophylactic bilateral mastectomy, breast cancer developed in 8 of 62 women in the surveillance group (12.9%) and 3 of 69 (4.3%) women in the oophorectomy group. The time to breast cancer or BRCA-related gynecologic cancer was longer (by Kaplan-Meier analysis and a Cox proportional-hazards model) in the salpingo-oophorectomy group, with a hazard ratio for subsequent breast cancer or BRCA-related gynecologic cancer of 0.25 (95% confidence interval, 0.08-0.74). Thus, Kauff et al concluded that salpingo-oophorectomy decreases the risk of breast cancer and BRCA-related gynecologic cancer for those who carry the BRCA mutations.

The second report in the same issue was a retrospective analysis of a large group (n = 551) of at-risk women (carriers of BRCA mutations) performed by Rebbeck and colleagues in the Prevention and Observation of Surgical End Points Study Group. Subjects were identified from registries and studied for the occurrence of ovarian or breast cancer. The group included 259 women who had undergone bilateral prophylactic oophorectomy and 292 matched controls who had not undergone the procedure. In a subgroup of 241 women with no history of breast cancer or prophylactic mastectomy, the incidence of breast cancer was determined in 99 women who had undergone bilateral prophylactic oophorectomy and in 142 matched controls. The length of follow-up for both groups was more than 8 years.

Six women who had undergone prophylactic salpingo-oophorectomy (2.3%) were found to have early stage ovarian cancer at the time of surgery. Subsequently, from this group, 2 women (0.8%) were found to have papillary serous peritoneal carcinoma 3.8 and 8.6 years after prophylactic oophorectomy. In contrast, 58 women (19.9%) received a diagnosis of ovarian cancer after a mean follow-up of 8.8 years. Excluding the 6 patients who were found to have cancer at the time of prophylactic oophorectomy, the procedure significantly reduced the risk of coelomic epithelial cancer (hazard ratio, 0.04; 95% confidence interval, 0.01-0.16).

Of the 99 women who underwent bilateral prophylactic oophorectomy and who were followed for the development of breast malignancy, breast cancer developed in 21 (21.9%) as compared with 60 (42.3%) in the control group (hazard ratio, 0.47; 95% confidence interval, 0.29-0.77). Thus, like the prospective study reported above, this larger, but retrospective analysis came to an identical conclusion: bilateral prophylactic oophorectomy reduces the risk of coelomic epithelial cancer and breast cancer in women with BRCA1 or BRCA2 mutations.

COMMENT BY WILLIAM B. ERSHLER, MD

Women who inherit certain mutations within the BRCA1 or BRCA2 genes face a 35-85% lifetime risk of developing breast cancer[1,2] and a 16-57% chance of developing ovarian cancer.[3] Genetic counseling and

medical or surgical interventions are likely to reduce these risks.

The data presented individually and in composite provide compelling support for the value of bilateral salpingo-oophorectomy in the prevention of both ovarian and breast cancer in women with BRCA mutations. The prospective study by Kauff et al was relatively small, nonrandomized, and of shorter duration. Over time, it is likely that there will be significant differences in the overall development of ovarian cancer in the different groups (as witnessed in the retrospective study that followed). The data for the prevention of breast cancer, derived from both of these reports, are quite solid. Prophylactic oophorectomy reduces breast cancer development in BRCA carriers, and curiously, it appears that both BRCA1 and BRCA2 carriers are similarly protected. This is in contrast to what might have been expected, inasmuch as BRCA1 carriers typically develop estrogen receptor negative tumors[4] and in at least 1 large primary prevention trial, the use of the antiestrogen Tamoxifen™ did not seem to protect BRCA1 carriers.[5]

A scientific methodologies purist might raise the concern that this is not a randomized or blinded study, but certainly the ethical concerns that would surround such an effort would be overwhelming and likely preclude ever getting useful data. In light of the larger, retrospective analysis from the Prevention and Observation of Surgical End Points Study Group, the findings are not only credible, but also clinically important.

The precise clinical implications from these reports remain to be determined. Of course there is a downside to oophorectomy (increased cardiovascular events, osteoporosis, etc), and yet, for women with such a high likelihood of developing either ovarian or breast cancer, it would seem in general that the benefits outweigh the risks. Issues that need to be taken on an individual basis until clinical trial data are available include the appropriate age for intervening, whether to include a hysterectomy, and whether some form of hormone replacement therapy will be allowable without undermining the beneficial effects of the oophorectomy. Furthermore, the data support the assessment of genetic susceptibility and referral for genetic counseling for all patients suspected to have BRCA mutations. The issues are complex, the variables are many, and discussions on the topic oftentimes raise very sensitive issues. The data from these reports will be useful for genetic counselors, BRCA carriers and their families as they consider the risks and weigh the options available to best prevent the development of either of these life-threatening diseases. ■

References

1. Easton DF, et al. *Am J Hum Genet.* 1995;56:265-271.
2. Antoniou AC, et al. *Genet Epidemiol*. 2000;18:173-190.
3. Struewing JP, et al. *N Engl J Med*. 1997;336:1401-1408.
4. Fisher B, et al. *J Natl Cancer Inst.* 1998;90:1371-1388.
5. King MC, et al. *JAMA*. 2001;286:2251-2256.

Novel Predictors of Androgen Independent Survival in Patients with Metastatic Prostate Cancer

ABSTRACT & COMMENTARY

Synopsis: There is currently no test which reliably assists in forecasting the duration of hormone dependence in patients receiving androgen ablative therapy for metastatic prostate cancer or for biochemical failure following attempted cure. Thus, predictions of the duration until development of hormone refractory disease are conjecture with little basis in science. Elimination of some or all of this uncertainty would benefit the clinical decision-making process. This study from Case Western Reserve performed a retrospective review of their patients maintained on androgen ablative therapy, and concluded that body mass index (BMI) and history of pathological fracture were novel, statistically significant, predictors of the duration of androgen independence and survival, respectively.

Source: Oefelein MG, et al. *Urology*. 2002;60:120-124.

Oefelein and colleagues performed a retrospective analysis of 184 consecutive prostate cancer patients who required androgen ablative therapy from 1986. There were 122 patients on monotherapy, 58 on total androgen suppression, and 4 who underwent orchiectomy. Median age was 72 years (range, 49-90), and median pretreatment PSA was 32 (range, 1.8-6033). One hundred twenty-six patients were white, 53 were African-American, and 5 were other. Reasons for initiation of androgen suppression were metastases to bone or lymph nodes (62%), or biochemical failure posttreatment (38%). Time to androgen independence was measured from the start of androgen suppression to the date of the first of 3 rising PSA values taken consecutively at 3-6 month intervals.

Eighty five patients (46%) became hormone refrac-

tory during the study period. Median overall survival for the entire group was 123 months. Median overall survival for patients started on therapy for a positive bone scan was 55%, and 89% for patients started on therapy for biochemical failures. Median time to development of hormone refractory disease was 44 months. It was 24 months for patients with bone metastases and 63 months for biochemical failure patients (P = .000001).

Significant factors for the development of hormone independent disease on univariate analysis were PSA nadir > 1, > 3 months to PSA nadir, pretreatment PSA > 50, > 44 months of androgen suppression, bone metastases, and BMI > 27 kg/m^2. Factors that did not reach significance were race, Gleason score, primary treatment, and history of pathologic fracture. Multivariate analysis revealed several factors that were predictive of the duration to androgen independence and survival, including PSA nadir > 1, > 3 months to PSA nadir, bone metastases, and BMI > 27 kg/m^2. In terms of which patients did the best, Oefelein et al found that slender patients who started with a biochemical failure and reached a PSA nadir in < 3 months had a median androgen dependent interval of 132 months, in comparison to heavy patients with bone metastases who never reached a PSA nadir, where the interval to androgen independence was only 15 months (P = .00001). Multivariate analysis evaluating factors predictive for overall survival found that bone metastases, pretreatment PSA, and history of pathologic fracture were significant (P < .05).

Oefelein et al concluded that BMI was a potentially important predictor of time to androgen independence, and that pathologic fractures were poor prognostic factors for overall survival. They pointed out that these 2 prognostic factors have not been previously recognized as clinically important in the setting of response to androgen ablation. A nomogram plugging in their institutional results, with + bone metastases on the y-axis and time to PSA nadir < 3 months vs. > 3 months on the x-axis, was provided and showed statistically significant differences in median time to androgen independence. Oefelein et al stated that prolonged, "possibly curative control" with androgen ablation exists in a subset of patients.

COMMENT BY EDWARD J. KAPLAN, MD

Surprisingly little is known about the optimal time to initiate androgen suppressive therapy, whether such therapy should be maintained on a continuous basis, or how one predicts the durability of response to androgen ablation. The intuitive notion that measurable disease, as in a positive bone scan or a pathologic fracture, or a high starting PSA, is worse is not surprising. It is also not surprising that patients whose disease is responsive to androgen ablation as reflected by a rapidly achieved and low nadir do better. Undetectable nadir PSA was also found to be significantly related to time to androgen independence by Benaim and colleagues from the University of Texas.[1]

Oefelein et al identified BMI as a new and potentially useful indicator of the duration of androgen independence for patients on ablative therapy. They referred to earlier work by others pointing to increased peripheral conversion of testosterone to estrogen in obese men as a risk factor for development of prostate cancer, and indicated that the same mechanism may be at work in their findings with BMI.

There were too few patients in the study to evaluate whether monotherapy was any more or less effective than combined androgen ablative therapy. Since all patients received continuous therapy, any contribution by intermittent androgen ablation was not evaluable. Oefelein et al, while postulating that BMI may be important based on serum testosterone levels, did not suggest that they were interested in measuring pretreatment serum testosterone in their patients. Perhaps focusing on percent body fat might be more to the point than BMI, since that seems to be where the conversion of testosterone to estrogen takes place. Along these lines, Vollmer et al analyzed data from 2 CALGB trials on hormone refractory prostate cancer patients, and found that patient weight was significantly related to survival.[2] Another very interesting finding by George et al from Dana Farber, also based on CALGB data, was that plasma vascular endothelial growth factor (VEGF) levels are significantly elevated in patients with hormone independent disease and inversely correlated with survival (P =. 002).[3]

Since BMI can be changed through dietary control, it is of interest to know whether BMI, weight, or percent body fat can alter a metastatic prostate cancer patient's prognosis. Furthermore, fat is a very metabolic tissue, and it likely has something to do with one's VEGF levels. For now, the nomogram shown by Oelefein et al may be useful in formulating treatment planning strategies when used in conjunction with other known prognostic factors such as pretreatment PSA. ■

References

1. Benaim EA, et al. *Urology.* 2002;59:73-78.
2. Vollmer RT, et al. *Clin Cancer Res.* 1999;5:831-837.
3. George DJ, et al. *Clin Cancer Res.* 2001;7:1932-1936.

Assessing the Predictive Value of Clinical Complete Response to Neoadjuvant Therapy for Rectal Cancer

ABSTRACT & COMMENTARY

Synopsis: In order to examine the accuracy of clinical evaluation, clinical and pathologic characteristics were compared for 488 rectal cancer patients who underwent preoperative chemoradiation. All patients were initially diagnosed with T3, T4, or node-positive disease based on physical exam or endorectal ultrasound. After neoadjuvant therapy and before resection, patients were re-examined clinically. Nineteen percent of patients had a complete response to neoadjuvant treatment based on preoperative clinical exam. Ten percent of patients had a complete response based on histologic exam of the resected specimen. Among the clinical complete responders, 25% had a pathologic complete response. Given its poor predictive value even in the hands of experienced clinicians, a clinical complete response must not preclude resection for rectal cancer patients.

Source: Hiotis SP, et al. *J Am Coll Surgeons.* 2002; 194(2):131-136.

The phenomenon of pathologic complete response (pCR) to neoadjuvant chemoradiation has led some investigators to question the dogma of surgical resection for nearly every solid tumor. Esophageal and rectal cancers are particularly amenable to preoperative chemoradiation and, thus, have been the focus of this controversy.[1,2] The caveat is that pCR cannot be known without resection. Champions of chemoradiation only must rely on a clinical determination of complete response (clinical complete response; cCR). To address this issue, Hiotis and colleagues examined the positive and negative predictive value of cCR compared with pCR among rectal cancer patients treated with chemoradiation followed by resection.

Four hundred eighty-eight patients who received neoadjuvant therapy for stage II or III disease were included; patients were excluded if they had evidence of a second primary lesion. Patients had T3, T4, or node positive rectal cancer by endorectal ultrasound (ERUS) or fixed lesions by digital rectal exam (DRE) and proctoscopy. Treatment regimens included 2 cycles of 5-fluorouracil-based therapy and > 50 Gy radiation, followed by surgery in 4-6 weeks, consistent with the 1990 NIH consensus panel recommendations.[3]

Clinical response to neoadjuvant therapy was determined within 1 week of operation, which generally took place within 6 weeks of chemoradiation, although some patients waited as long as 12 weeks. A designation of cCR was given if no residual tumor could be identified by DRE or proctoscopy. Pathologic response was determined using standard methods to examine resected specimens. A designation of pCR was given to those specimens with bowel wall entirely absent of viable tumor cells. Chi square analysis was used to compare cCR and pCR rates.

The cCR rate was 19% (93/488); pCR rate was 10% (50/488). Among patients with cCR, 25% (23/93) had a pCR. That is, the positive predictive value of cCR = 25%. Among patients without cCR, 93% (368/395) also did not have pCR. That is, the negative predictive value of cCR = 93%. Notably, 4 patients with remaining node-positive disease on pathologic exam did not have residual tumor in bowel wall and were thus designated pCR.

Given the poor positive predictive value of cCR, even in the hands of experienced colorectal surgeons, Hiotis et al recommend that all stage II and III rectal cancer patients continue to undergo resection.

COMMENT BY ARDEN MORRIS, MD

Focusing on rectal cancer, Hiotis et al address the recurrent question of when resection can be safely avoided. As in a host of previous studies, clinical evaluation proved inaccurate for assessing residual disease. However, PCR to neoadjuvant therapy is an encouraging phenomenon and deserves further careful study. Given the limited available evidence, the addition of postadjuvant preoperative ERUS, CT, or even MRI may not improve the positive predictive value of clinical assessment.[4] Further study of these modalities and of PET scan in this setting is warranted.

Additionally, the implications of pCR are not completely understood. Long-term follow-up of pCR patients (who have, by definition, undergone resection) is still being gathered and recurrence rates, potentially from missed micrometastases, are unknown. Furthermore, if technology-enhanced determination of cCR can be closely correlated with pCR, future decisions to avoid resection would be based on outcomes of pCR patients who may have had residual unrecognized disease removed.

Still the impetus to eliminate surgical resection from the treatment of rectal cancer when possible is based upon worthy motives. Patients' postoperative quality of life, risks of morbidity and mortality, and

medical costs are important counters to the benefit of operation and must be acknowledged. For a few solid tumors, such as small cell carcinoma of the lung, squamous cell cancer of the anus, and some small squamous cell cancers of the head and neck, chemoradiation has been so successful that operation may often be virtually eliminated from the treatment regimen. For now, however, surgical resection remains the mainstay of treatment for rectal cancer and for most stage I-III solid tumors. ■

References

1. Coia LR, et al. *J Clin Oncol*. 2000;18:455-462.
2. Habr-Gama A, et al. *Dis Colon Rectum*. 1998;4: 1087-1096.
3. NIH. *JAMA*. 1990;264:1444-1450.
4. Kahn et al. *Dis Colon Rectum*. 1997;40:140-144.

Oncologists' Attitudes Toward and Practices in Giving Bad News: An Exploratory Study

ABSTRACT & COMMENTARY

Synopsis: There is significant variability in how physicians approach information disclosure to cancer patients.

Source: Baile WF, et al. *J Clin Oncol*. 2002;20: 2189-2196.

To examine the attitude of oncologists in disclosure of unfavorable medical information to cancer patients, Baile and colleagues administered a questionnaire to a group of physicians who attended the 1999 Annual Meeting of the American Society of Clinical Oncology. The questionnaire assessed demographic and practice-related information and the frequency of patient encounters in which unfavorable cancer-related information was disclosed. Participants were also asked about difficulties they had when approaching stressful discussions and communication strategies used in giving unfavorable information. The questionnaire was completed by 167 oncologists. Sixty-four percent were medical oncologists. Thirty-eight percent practiced in North America, 26% practiced in Europe, 13% practiced in South America, and 13% practiced in Asia. Participants gave bad news to patients an average of 35 times per month. Discussing no further curative treatment and hospice was reported as most difficult. In disclosing the cancer diagnosis and prognosis, physicians from Western countries were less likely to withhold unfavorable information from the patient at the family's request, avoid the discussion entirely, use euphemisms, and give treatments known not to be effective so as not to destroy hope than physicians from other countries. There was significant variability in opinions regarding the best time to discuss resuscitation, with 18% of respondents believing that it should be done close to the end of life. They concluded that there was significant variability in how physicians approach information disclosure to cancer patients. Factors such as geographical region and cultural and family variables may be important influences in this process.

■ COMMENT BY DAVID M. GERSHENSON, MD

Baile et al have been among the international leaders in the area of "breaking bad news." They and others have been extremely active in conducting formal courses and workshops and developing guidelines for giving bad news to cancer patients and their families. This paper highlights several important aspects of physician-patient communication. There are still major cultural differences in the information provided to patients and their families between Western and non-Western physicians. Non-Western physicians are more likely to avoid discussing prognosis, to withhold information from the patient at the family's request, and to offer patients futile treatments to preserve hope. However, Western physicians also face several challenges regarding giving unfavorable news. The most problematic areas are providing information about a poor prognosis and the timing of providing counseling about "do not resuscitate" orders, discontinuing therapy, and hospice care. My sense is that most oncologists, including myself, broach the latter set of issues much too late in the course of many patients' care. In addition to cultural differences, this study explored gender differences. And it is no surprise to me that women were more adept at discussing hospice care and other difficult issues than men. As Baile et al point out, further research is needed in this area. One strategy that is gaining popularity is to query newly diagnosed patients on very specific issues related to how much she wants to know prior to the physician consultation. In this manner, the patient can actively participate in the decision concerning prognostic information, the stickiest issue for most oncologists. ■

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

CME Questions

11. Which of the following regarding time to androgen independence in the Oelefein paper is *false*?

a. Patients on combined therapy did just as well as those on monotherapy.
b. Gleason score did not show a statistically significant impact.
c. BMI was not a statistically significant predictor of time to androgen independence.
d. All of the above

12. Regarding the Oelefein paper, which statement is correct?

a. Patients with slow times to PSA nadir did as well as those with rapid times to nadir.
b. Patients with rapid times to PSA nadir had outcomes equivalent to those with slow times to nadir.
c. Patients with rapid times to PSA nadir did better than those with slow times to nadir.
d. Time to PSA nadir was not a statistically significant factor.

13. Which of the following statements about prophylactic salpingo-oophorectomy for the prevention of breast cancer is true?

a. This procedure has been shown to be associated with reduced rates of ovarian and breast cancer if performed in ALL patients with a family history of breast cancer.
b. This procedure has been shown to be associated with reduced rates of ovarian and breast cancer in BRCA1 but not BRCA2 mutation carriers.
c. This procedure has been shown to be associated with reduced rates of ovarian and breast cancer in BRCA2 but not BRCA1 mutation carriers.
d. This procedure has been shown to be associated with reduced rates of ovarian and breast cancer in both BRCA1 and BRCA2 mutation carriers.

14. Nonsurgical therapy is the treatment of choice for which of the following carcinomas?

a. Lymphoma of the stomach.
b. Adenocarcinoma of the rectum, after a complete clinical response to neoadjuvant chemoradiation.
c. Adenocarcinoma of the esophagus after a complete clinical response to neoadjuvant chemoradiation.
d. Squamous cell carcinoma of the true vocal cord.

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Clinical Oncology Alert*. Send your questions to: Robert Kimball, Clinical Oncology Alert, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Clinical Oncology Alert* via the internet by sending e-mail to robert.kimball@ahcpub.com. ■

In Future Issues:

Hormone Replacement Therapy—What Now?