AMERICAN HEALTH CONSULTANTS® A Medical Economics Company

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

The Site of BCL-2 Rearrangement in Follicular Lymphoma May Influence Prognosis

ABSTRACT & COMMENTARY

Source: Lopez-Guillermo A, et al. *Blood* 1999;93:3081-3087.

In a number of malignancies characterized by chromosomal translocations, heterogeneity in the molecular features of the translocation has been examined for its influence on prognosis. For example, in patients with the t(9;22) translocation and chronic myeloid leukemia, the translocation involves the juxtaposition of the abl gene on chromosome 9 with the bcr gene on chromosome 22. However, the site of the break on chromosome 22 is variable. The vast majority of breaks occur within a 5.8 Kb long region that has been called the major breakpoint cluster region (Mbcr). When the break occurs toward the 3' end of the Mbcr, the chimeric gene created contains exon 3 of bcr (the gene product is called a2b3 to signify the joining of the second abl exon with the third exon of bcr). When the break occurs more 5', exon 3 of bcr is deleted and the a2 exon is fused to the b2 exon creating a2b2. A couple of reports[1] suggested that patients with a 3' break might have a shorter chronic phase than those with a 5' break. However, most investigators have not found any clinical correlation between the chromosome 22 breakpoint and prognosis.[2-4]

Similarly, the t(14;18) translocation in follicular lymphoma is characterized by heterogeneity in the chromosome 18 breakpoint. About two-thirds of the rearrangements occur at the major breakpoint region (MBR) located in the 3' untranslated portion of the last exon, about 10% occur in the minor cluster region (mcr) located about 30 Kb downstream of the bcl-2 gene, and in the remaining cases (about 15%), no translocation is detected by any technique. The efforts to relate the molecular anatomy of the translocation to prognosis have generally failed to reach firm conclusions because of heterogeneous histologic diagnoses (some papers included cases of diffuse large B-cell lymphoma of follicular center origin), heterogeneous treatments, small numbers of cases (< 100), and failure to take into account the distribution of other possibly independent prognostic factors such as performance status, lactate dehydrogenase levels, and others.

Lopez-Guillermo and colleagues at M.D. Anderson Cancer Center have analyzed breakpoints in 247 patients with follicular lymphoma who were treated mainly with anthracycline-based combination chemotherapy. It is difficult to be certain, but these patients appear to have been treated mainly before the use of fludarabine in follicular lymphoma. The breakpoints occurred in the MBR in 175 patients (71%), in the mcr in 27 patients (11%), and no rearrangement was detected in 45 patients (18%). No significant differences were noted in the expression of bcl-2 or bax proteins. No significant differences were seen in the clinical characteristics. However, patients with either type of translocation had a significantly higher complete response rate (mcr 96%, MBR 90%) than did patients with germline tumors (71%). Failure-free survival at three years was also different among the groups: mcr tumors had the best outcome, 95% were failure-free at three years; for MBR, 76%; and for germline, 57%. When patients were stratified on the basis of lactate dehydrogenase levels and beta-2-microglobulin levels, the number of patients became much smaller, but the relationships among the three groups were retained and a Wilcoxon test gave a P-value of 0.08, implying that the type of rearrangement was largely independent of these other risk factors.

COMMENTARY

On the basis of this report, Lopez-Guillermo et al would order the prognosis of patients with follicular lymphoma based upon the nature of the translocation as follows: mcr > MBR > germline. Almost no one with mcr fails to achieve a complete response or relapses, but this form is rare. Those with MBR comprise the majority of cases and they follow the typical follicular lymphoma relapse curve with a steady rate of relapse without hint of a plateau. Those without rearrangements respond poorly to therapy, and their relapse curve resembles that associated with aggressive histology lymphoma. The relapses that occur usually happen within the first year and those in remission at three years after treatment appear less likely to relapse.

It is difficult to know how to interpret these data. While intriguing, it is not obvious why the subsets should be different. They all overexpress bcl-2 protein, and it is clear that bcl-2 overexpression is not sufficient to cause this neoplasm. It is possible that the different subsets are associated with a distinct pattern of mutations in other genes. But such an analysis has not yet been undertaken. If the subsets do differ in the spectrum of genes that are mutated, it would be difficult to attribute the difference to the bcl-2.

However, this level of ignorance is not the most pressing matter. What is most important is to define whether these observations are true; because if they are true, then no mcr patient should have treatment withheld, and those with MBR and germline genetics should be stratified and balanced in any future study as their prognosis is different. It would be valuable to try and ascertain the reproducibility of these findings in a group of patients like those who have been treated conservatively at Stanford over the years. Is the natural history of the subsets really distinct? Would patients who have been watched without treatment for 10 years or more disproportionately be those with mcr rearrangements?

It appears that therapy for follicular lymphoma is improving. The fludarabine-based combinations appear to be capable of inducing molecular-complete remissions in the majority of treated patients, and such remissions appear to be more long-lasting than remissions from other types of chemotherapy. Furthermore, the introduction of rituximab promises to further enhance the efficacy of the treatment in that the antibody may sensitize cells to the chemotherapy.[5] It would be important to know whether there are molecular markers that could distinguish subsets of patients who do well, and those for whom a different approach would be indicated. Molecular characterization of the bcl-2 break-

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.
EXECUTIVE EDITOR: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
ASSISTANT MANAGING EDITOR: Robin Mason.
COPY EDITORS: Holland Johnson, Neill Larmore, Michelle Moran.
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: $33.
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.

Dr. Longo's work as an editor and author was performed outside the scope of his employment as a U.S. government employee. This work represents his personal and professional views and not necessarily those of the U.S. government.

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail Address:
customerservice@ahcpub.com
Editorial E-Mail Address:
holland.johnson@medec.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$199 per year (Student/Resident rate: $100).
Multiple Copies
1-9 additional copies: $100 each; 10 or more copies: $60 each.
Canada
$243 per year including GST (Student/Resident rate: $110 including GST).
Elsewhere
$229 per year (Student/Resident rate: $110).

Accreditation

American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor CME for physicians. American Health Consultants designates this CME activity for 20 credit hours of Category 1 of the Physician's Recognition Award of the AMA. This CME activity was planned and produced in accordance with the ACCME Essentials.
For 20 Category 1 CME credits, add $50

Questions & Comments

Please call Robin Mason, Assistant Managing Editor, at (404) 262-5517 or Holland Johnson, Copy Editor, at (404) 262-5540 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

American Health Consultants does not receive material commercial support for any of its continuing medical education publications. 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. Longo is a consultant to Coulter and Pharmacia-Upjohn and is a stockholder of Bristol-Myers Squibb and Merck. Dr. Chabner is a consultant for Pharmamar, Eli Lilly, and Genzyme, is a stockholder of Immonex and does research for Kirin-Amgen, Smith Klein, Rhone-Poulenc, Merck, Bristol Myers Squibb, and Genzyme. Dr. Lippman is a consultant for Technicione, Procept, Genta, Eli Lilly, Abbott, Quest, Seattle Genetics, and Strategene Genomics and is a stockholder of Technicione, Genta, Lilly, Merck, and Bristol Myers Squibb and is on the Speaker's Bureau for Amgen. Dr. Young is a consultant for Bristol Myers Squibb and Berlex.

point is an intriguing lead that needs to be followed up, but support for its role has not yet reached the level of evidence for practice to be modified on its basis. ❖

References

1. Mills KI, et al. *Leukemia* 1989;3:837-840.
2. Jaubert J, et al. *Br J Haematol* 1990;74:30-35.
3. Tefferi A, et al. *Leukemia* 1990;4:839-842.
4. Opalka B, et al. *Leukemia* 1991;5:452-456.
5. Czuczman MS, et al. *J Clin Oncol* 1999;17:268-276.

Preoperative CT Scans and Node-Positive Gastric Cancer

ABSTRACT & COMMENTARY

Synopsis: *The presence of lymph node metastases as determined histologically has proven to be an excellent indicator of prognosis in patients with gastric cancer. Seventy-eight patients were studied to evaluate the ability of preoperative CT scanning to predict surgical findings and prognosis. The level of lymph node metastases was graded as level I (perigastric nodes), level II (intermediate nodes along the left gastric, common hepatic and celiac arteries, or level III (distant nodes). Nodal status, as determined by CT was a good predictor of prognosis. Thus, the one-year survival for those with level I nodes was 55%, compared to 27% for those with level II and 7% for level III. CT-determined lymph node status offers important prognostic information in patients with gastric cancer.*

Source: Adachi Y, et al. *J Clin Gastroenterol* 1999;28: 140-143.

The presence of lymph node metastases as determined by microscopic examination of surgical specimens has been recognized as an important prognostic indicator in gastric carcinoma. However, the value of determining lymph node metastases by computed tomography (CT) remains unknown. In the current report 78 patients were described. These were drawn from a population of patients who were seen at the First Department of Surgery, Oita Medical University in Japan. The level of lymph node metastases, as assessed by CT were graded as level-I, perigastric nodes; level-II, intermediate nodes along the left gastric, common hepatic, and celiac arteries; and, level-III, distant nodes along the hepatoduodenal ligament, pancreas, spleen, and abdominal aorta.

Sixty patients (79%) had stage IV tumors. For the whole group, one- and five-year survival rates were 29% and 6% respectively, and the one-year survival rate was significantly influenced by the level of lymph node metastases as demonstrated by CT scan (55% for level-I, 27% for level-II, and 7% for level-III; $P < 0.01$). In those patients who underwent gastrectomy, prognostic factors were tumor size (< 10 cm vs. > 10 cm), gross type (localized vs infiltrative), and histologic type (well-differentiated vs poorly-differentiated).

Adachi and colleagues suggest that the prognosis of patients with CT-assessed node-positive gastric carcinoma is poor because of the high frequency of extensive tumor spread. However, patients having only positive level-I (perigastric) nodes on CT remain candidates for curative gastrectomy, which offers the possibility of long-term survival.

COMMENTARY

Perhaps the value of this study relates to the apparent correlation of CT scan noted lymphadenopathy and overall outcome. At surgery, lymph nodes that were found to be enlarged on CT scan were likely to harbor disease (more than 3/4 of the cases confirmed positive). Furthermore, the one-year survival rate was significantly influenced by the level of lymph node metastasis as determined by CT scan.

It is not unexpected that the presence or absence of lymph node metastases would have important predictive value with regard to survival in patients with gastric cancer.[1] In fact, the number or level of lymph node metastases has proven to be significant in previous work. [2,3] However, those results were based upon data from operated patients and, thus, may represent a selected group. Furthermore, many of those patients had histologic assessment of lymph nodes but unresectable gastric tumors. Data from the current study may offer predictive value regarding those patients for whom laparotomy has the greatest chance to result in curative resection (i.e., those patients with no, or only level I adenopathy). In contrast, patients with advanced disease (e.g., level-III adenopathy) probably should not be treated by aggressive surgical intervention, for survival is extremely low. Consideration of quality-of-life issues in these patients would seem most appropriate and avoiding the morbidity of aggressive surgery would have clinical value.

This series highlights the potential importance of careful CT scanning in patients with gastric cancer. Patients with level I metastases remain good candidates for laparotomy. Those found preoperatively to have more extensive adenopathy may be better treated with palliative, limited surgery or with nonsurgical approaches. It remains to be seen whether preoperative chemotherapy and radiation therapy (neoadjuvant therapy) might convert some patients with level II or III

adenopathy by CT scan to level I adenopathy with the attendant improvement in prognosis and in the chances of success from a more aggressive surgical approach. ❖

References

1. Bozzetti F, et al. *Surg Gynecol Obstet* 1986;162: 229-234.
2. Gunven P, et al. *Br J Surg* 1994;78:352-354.
3. Adachi Y, et al. *Br J Surg* 1994;81:414-416.

The True Skinny on Ultrasound-Guided Fine-Needle Aspiration of Nonpalpable Breast Lesions

ABSTRACTS & COMMENTARY

Synopsis: *The National Cancer Institute (NCI) has developed a uniform reporting system for fine-needle aspiration (FNA) of the breast. In this series, a retrospective evaluation of archival FNAs was categorized using the new NCI system. Ultrasound-guided FNA, as reported by the new NCI guidelines, is both a sensitive and specific means to diagnose nonpalpable breast cancers.*

Sources: Boerner S, et al. *Cancer* 1999;87:19-24; Masood S. *Cancer* 1999;87:1-4.

Because of substantial heterogeneity in technique, terminology, and clinical interpretation, the National Cancer Institute (NCI) supported the development of specific diagnostic categories for fine-needle aspiration (FNA).[1,2] In this system, FNAs are classified into one of five categories: 1) benign; 2) indeterminate/atypical; 3) suspicious/probably malignant; 4) malignant; or 5) unsatisfactory. In this report from Boerner and colleagues, the NCI system was applied to a large number of archival samples and the interpretations were compared to subsequent biopsies and clinical outcomes.

Ultrasound-guided FNAs (US-FNAs) performed on nonpalpable breast lesions between the years 1988 and 1996 at M.D. Anderson Cancer Center were reexamined using the new NCI system. There were 1855 US-FNAs performed on 1639 patients during this period. The original FNA diagnoses were reclassified into the NCI categories, and the findings were correlated with the tissue specimens available in 851 cases or, with the clinical follow-up in those with FNA findings of benign lesions.

Of the 1885 cases, 56% were benign, 4.6% were atypical, 4.2% suspicious, probably malignant, 27% were malignant, and 8.5% unsatisfactory. Those that were benign included 45% cysts and 55% solid lesions. Of those categorized as benign, 3.7% (n = 13) were found by subsequent surgical specimen or clinical course to be malignant. Of those categorized as atypical, 53% were found to be malignant, whereas 76% of those categorized as suspicious were found to be malignant. Of the malignant FNAs, 1% of the lesions were found to be benign. Based upon the subsequent histologies and clinical follow-up, a sensitivity of 97.1% and a specificity of 99.1% were found for US-FNAs when definitive benign and malignant diagnoses were offered. The false-negative ratio of 3.7% was attributed to sampling error whereas the false-positive rate of 0.68% was thought secondary to interpretive error of proliferating lesions.

Boerner et al conclude that the application of the NCI-supported diagnostic categories to US-FNA of nonpalpable breast lesions is useful in stratifying aspirates with regard to the likelihood of indicating malignancy and thereby provides a rationale for the use of this approach, coupled with clinical exam and imaging studies for patients with possible breast cancer.

COMMENTARY

FNAs have received a lot of attention and increasing use, but inconsistencies in technique and interpretation have often left clinicians confused and patients misinformed. The new NCI guidelines may be of great value, but there have been limited large series published in which clinical outcomes have been correlated with their application. In this report, a special subset of patients, those with nonpalpable lesions, were reported. This reflects a difficult population and one in which precise and accurate sampling could save more invasive intervention. Indeed, as indicated in this retrospective series, over 50% of the FNAs resulted in a benign diagnosis and, presumably, clinical follow-up alone without biopsy would be sufficient management. Only 3.7% of patients with a nonmalignant diagnosis on FNA went on to develop cancer. In contrast, 26% of the FNAs resulted in an unequivocal malignant diagnosis. These patients would have also benefited since the FNA may well have spared them an open biopsy, and thereby allowed the direct initiation of definitive therapy. It has not been determined whether the 9% of patients within the intermediate categories of atypical or suspicious are actually benefited by that information. This study would suggest that about half of the 4.2% of patients in the atypical category, and about three-fourths of the 4.6% in the suspicious category will be found to have malignancy. Essentially all of these patients will need to

proceed to biopsy for definitive diagnosis. However, the number of patients who must go on to biopsy is only about 17% of the total; the 9% with atypical or suspicious cytology and the 8% in whom the aspirate was technically inadequate.

Yet, for patients and clinicians, what is worrisome is the possibility of false negatives (and false positives) for diagnostic procedures such as FNA. The NCI strategy does help in this regard because it differentiates between the unequivocal benign and malignant categories, and about 75% in this series fell into one of those two categories. Even in expert hands, there were 13 patients (3.7%) who were incorrectly reassured that their breast lesions were benign, and an additional three patients were taken to surgery because they were told their lesions were malignant, only later to be informed that this was an error. With a disease such as breast cancer where fears and emotional tensions are inherently at a high pitch, even these small numbers are difficult to accept, and may have medical-legal consequences.

Nevertheless, the NCI guidelines are helpful, they allow better communication and uniformity of treatment between physician groups at different institutions. It is now the challenge for those in this field to further improve the reliability of minimally invasive diagnostic strategies, and to define the optimal management strategies for patients with nonpalpable breast masses who are diagnosed on the basis of FNA. ❖

References

1. Anonymous. *Acta Cytol* 1996;40:1120-1126.
2. Anonymous. *Breast J* 1997;3:149-168.

Interleukin-10 Staining Provides Important Prognostic Information in Nasopharyngeal Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Nasopharyngeal cancer cells were shown to express IL-10 by immunohistochemistry. The results of this study imply that expression of IL-10 is a prognostic factor in patients with nasopharyngeal cancer and may prove useful in development of treatment strategies.*

Source: Fujieda S, et al. *Cancer* 1999;85:1439-1445.

Interleukin-10 (il-10) is an important modulator of lymphocyte function with generally immunosuppressive properties.[1] Its production by a variety of tumor cells including lymphoma[2] and melanoma[3] has been associated with more aggressive tumor characteristics, and shortened survival. The association between Epstein-Barr virus (EBV) and nasopharyngeal carcinoma (NPC) has been appreciated for two decades. Recently, EBV-encoded RNA signals were identified in nuclei of malignant cells in 96.4% of primary NPC tumors.[4] It has now also been appreciated that the EBV genome produces a protein (designated viral-IL-10) with extensive homology to human IL-10, and like human IL-10, v-IL-10 inhibits cytokine production by human peripheral blood mononuclear cells.[4]

In this report, Fujieda and colleagues investigated the expression of IL-10 in 21 primary nasopharyngeal cancers using immunohistochemical techniques. IL-10 staining was positive in 12 of 21 (57%). There was no association between IL-10 expression and gender, tumor size, the occurrence of lymph node metastases, clinical stage, or recurrence. However, there was a significant difference in overall survival between those that stained negative and positive for IL-10. Although 87% of the IL-10 negative group survived for five years, only 15% of the IL-10 positive patients survived that long. Using multivariate analysis, IL-10 expression was significant as an independent prognostic indicator of overall survival. Fujieda et al propose that IL-10 staining of primary NPC may be useful in selecting patients at all stages for aggressive treatment.

COMMENTARY

Fujieda et al found that there was a bimodal distribution of IL-10 expression in tumors from patients with NPC. An IL-10 staining score of less than 10% was considered negative, whereas a score of more than 30% was positive. The IL-10 score in patients with Stage IV disease was higher than those with Stage II or Stage III, but this difference was not significant by one-way analysis of variance. Furthermore, there was no association between IL-10 expression and tumor size, lymph node status, clinical stage, or recurrence. Yet, the IL-10 score was significantly correlated with death from disease. Nine patients died of disease in this study, and their IL-10 staining score was 65%, compared to a score of 28% in those who survived.

Thus, IL-10 staining was a useful independent prognostic indicator in patients with NPC. Why this would be the case is a matter of conjecture. However, it might relate to the function of IL-10, which is generally immunosuppressive. Not only does IL-10 inhibit other cytokine production, it has been shown to inhibit specific T-cell functions, antigen presentation, and

macrophage function in various tumor immunity models.[5-7] A local production of IL-10 within the NPC microenvironment might undermine local immune or inflammatory responses that would otherwise inhibit growth.

Another proposed mechanism of tumor-enhancement by IL-10 relates to its potential as a direct growth factor. For example, melanoma cells have been shown to express both IL-10 and IL-10 receptor, and anti IL-10 antibody decreased spontaneous proliferation of cells.[8] This would suggest that IL-10 might function as an autocrine growth factor for melanoma. Whether this is true for other tumor types, such as NPC, remains to be investigated.

Finally, IL-10 staining in NPC tumors may well relate to its association with EBV. The strong association with IL-10 expression and patient survival suggests that its immunosuppressive, or direct tumor- enhancing properties, may be of clinical importance. High tumor IL-10 expression was found in approximately one-half of NPC patients, and it was a strong, independent predictor of survival. Clinicians and clinical investigators might benefit from assessing this tumor characteristic when developing treatment strategies. ❖

References

1. Malefyt RW, et al. *J Exp Med* 1991;174:915-924.
2. Blay JY, et al. *Blood* 1993;82:2169-2174.
3. Sato T, et al. *Clin Cancer Res* 1996;2:1383-1390.
4. Tsai ST, et al. *Cancer* 1996;77:231-236.
5. Kim J, et al. *J Immunol* 1995;155:2240-2247.
6. Qin Z, et al. *J Immunol* 1997;159:770-776.
7. Lacraz S, et al. *J Clin Invest* 1995;96:2304-2310.
8. Yue FY, et al. *Int J Cancer* 1997;71:630-637.

Special Feature

DNA Tests and Risk Assessment

By Joann Bodurtha, MD, MPH, FACMG, and Thomas J. Smith, MD, FACP

Five years have elapsed since the announcement of the discovery of the BRCA1 gene. The science of testing is getting more complicated. The gene is large and many different mutations can occur. The differences between pathogenic mutations and "neutral" changes, or polymorphisms, may not be clearcut. Other genes for hereditary breast cancer susceptibility (e.g., BRCA2) have also been found.

Table 1

Germline BRCA1 Mutations in Select Populations

Population Studied	% with Germline Mutations
High-risk Families	12.8 - 39
Early-onset breast cancer	
Non-Jewish women	6.2 - 13
Jewish women	21 - 50
Population-based	0 - 9.1
Clinic-based	7 - 40

Adapted from: Hartge P, et al. *Am J Hum Genet* 1999;64:963-970.

The implementation of testing is complicated. Patents, and a limited array of research protocols, have discouraged a one-stop shopping approach. Physicians have variable comfort and skill in addressing family history and time-consuming informed consent. They share women's concerns about emotional distress, employment and discrimination issues, cost, and the "so what can I do differently with this information?" question. We address five related questions here.

How likely am I to find a BRCA1 mutation in a patient with breast cancer?

More than 80% of women with breast cancer do not have a family history. The presence of multiple occurrences of breast and ovarian cancer before age 50 in a family increases the chances that a mutation will be found. Estimates of the prevalence of mutations in BRCA1 and BRCA2 from series of patients with breast or ovarian cancers, registries of families with multiple episodes of these cancers, and community samples are shown in Table 1. (*See Table 1.*) Three founder mutations in BRCA1 and BRCA2 occur frequently enough among Ashkenazi Jews to enable consideration of this specific testing. Community samples of 5318 Jewish women and men in the Washington DC area found that 2.3% carried one of these mutations. Among 297 women with breast or ovarian cancer, 9.1% carried a mutation.[1]

How likely is a person with a BRCA1 or BRCA2 gene change to develop cancer?

The Breast Cancer Linkage Consortium has estimated the risks of breast cancer conferred by BRCA1 mutations to be about 50% by age 50 years and about 85% by

age 70 years. In the Washington Ashkenazi Study, the risk of developing breast cancer by age 70 was estimated to be 13% in non carriers of the three common mutations and 56% in carriers.

Cumulative risks at age 70 years were 13% for ovarian cancer and 16% for prostate cancer in carriers. The interaction of these genes with other genes and environmental risk factors is likely to make individualized risk prediction complex.

How are people deciding to refer for genetic counseling and testing?

The recently NCI-funded Cancer Genetics Network hopes to understand better what is actually happening in oncology practice, not only what is occurring in research protocols. In part because genetic counseling and testing are variably covered by insurance, some amount of self-selection and limitation of access exists *a priori*.

Some health maintenance organizations have developed triage plans for referral. The Permanente Medical Group criteria for referral for genetic screening include:

- persons with a known clinically-significant BRCA gene change in a relative
- persons with multiple primary breast tumors
- persons with breast and ovarian cancer
- Ashkenazi Jewish descent and ovarian cancer, or having breast cancer at younger than 40 years and Ashkenazi Jewish descent and having breast cancer at younger than 30 years.[2]

For women younger than 50 years with breast cancer, they suggest that one or more first- or second-degree relatives with breast cancer diagnosed younger than age 50 be present. Additional parts of their algorithm address other family history issues, men, significant anxiety, and ovarian cancer (Permanente Medical Group). All individuals are required to have genetic counseling and sign a formal informed consent document prior to genetic testing.

Any list is acknowledged to become dated, but the ASCO curriculum for Cancer Genetics and Cancer Predisposition Testing (1998) considers three groups in its guidelines for testing. (*See Table 2.*)[3]

Table 2

ASCO Cancer Genetics and Predisposition Guidelines by Group

Group 1. Genetic test result will change medical care and is standard management. Examples: familial adenomatous polyposis, multiple endocrine neoplasia 2, multiple endocrine neoplasia 1, retinoblastoma, Von Hippel-Lindau disease.

Group 2. Possible medical benefit in the identification of a germline mutation. Examples: hereditary nonpolyposis colorectal cancer, hereditary breast and ovarian cancer, Li-Fraumeni syndrome, Cowden syndrome.

Group 3. Tests in which the significance of the detection of a germline mutation is not clear; or for which mutations have been identified only in a small number of families. Examples: melanoma and associated syndromes, Wilms tumor, familial papillary renal carcinoma, Peutz-Jeghers syndrome.

Adapted from: ASCO,1998.

Where do I find a genetic counselor to refer my patients?

Several resources are available for finding cancer genetics professionals. They include: The National Cancer Institute's Cancer Genetics Professional Directory at *http://cancernet.nci.nih.gov/wwwprot/genetic/generch.html*, and the National Society of Genetic counselors at *http://www.nsgc.org/Resource_link.html*. The Cancer Information Service (1-800-4-CANCER) is also developing as a resource for information about cancer genetics professionals and cancer genetic research. The National Society of Genetic Counselors can also be reached at 610-872-7608 and by e-mail *NSGC@aol.com*.

Our prediction is that most oncologists will opt not to do this in the office (it will be too time-consuming, scientifically challenging, and not reimbursed like chemotherapy).

What is on the horizon for cancer susceptibility testing?

The DNA chip offers the potential for automated multiple mutation testing. It seems likely that it will first be used for individuals with a particular cancer or genetic condition to screen more efficiently for their specific mutation. Relatives could decide when to order their chip home test kit as can now happen for cystic fibrosis mutation testing in England.

The history of genetic screening, for example with metabolic conditions like phenylketonuria (PKU) in newborns and alpha-fetoprotein in pregnant women, suggests that some specific interventions need to have broad public support before the screening is adopted widely.

We foresee that offering testing to women younger than 50 years of age who present with breast cancer may effect surgical and chemotherapy choices as data from ongoing clinical trials becomes available. Maybe those who are BRCA1 or 2 positive will be able to go on tamoxifen as one way of successfully preventing new cancers. Genetic cancer susceptibility testing might be

incorporated with the annual Pap exam, stool blood test, or mammography screening. ❖

References

1. Hartge P, et al. *Am J Hum Genet* 1999;64:963-970.
2. Permanente Medical Group (1997). Clinical Practice Guidelines for Referral for Genetic Counseling for Inherited Susceptibility for Breast and Ovarian Cancer. Copies available by calling 510-987-2950.
3. American Society of Clinical Oncology curriculum information may be obtained through ASCO, 225 Reinekers Lane, Suite 650, Alexandria VA 22314.
4. Couch F, Hartman L. *JAMA* 1998;279:955-957.

CME Questions

23. Interleukin-10 expression in primary nasopharyngeal cancers has been shown to:

a. correlate with primary tumor size.
b. correlate with lymph node status.
c. correlate with patient survival.
d. all of the above.
e. none of the above.

24. Which of the following statements about fine needle aspiration of nonpalpable breast lesions is true?

a. Its value is diminished because close to 50% of interpretations fall into the "atypical" category for which appropriate management is uncertain.
b. In expert hands, a "malignant" interpretation is a reliable finding (close to 99% predictive value).
c. An "atypical" interpretation has a greater likelihood of reflecting a malignant lesion than a "suspicious" interpretation.
d. Even in expert hands, a "benign" interpretation has about a 10% chance of being an error.
e. Regardless of the result of FNA, a biopsy is necessary to confirm the result.

25. Which of the following statements about lymph node metastases in gastric cancer is true?

a. Enlarged nodes by CT are commonly "reactive" and actually harbor metastatic cells in less than 25% of cases.
b. Neoadjuvant chemotherapy has been proven to cause level III adenopathy regress to level I adenopathy and permit a potentially curative resection.
c. Perigastric nodes (level I) may be present in patients for whom potentially curative resection is still a possibility.
d. Advanced nodal disease (level III), but without distant organ metastases, may be present in patients for whom potentially curative resection is still a possibility.
e. CT scans are not useful preoperatively in patients with gastric cancer, but can be of clinical benefit for follow-up postoperatively to determine local or metastatic disease.

26. Which of the following statements about bcl-2 gene translocations in follicular lymphoma is true?

a. Those with breakpoints in the minor cluster region (mcr) appear to have the best prognosis.
b. Those with breakpoints in the mcr appear to have the worst prognosis.
c. Those with breakpoints in the major breakpoint cluster (MBR) appear to have the best prognosis.
d. Those with breakpoints in the MBR appear to have the worst prognosis.
e. Those with germline bcl-2 appear to have the best prognosis.

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: Holland Johnson—Reader Questions, 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 holland.johnson@medec.com.

You can also visit our home page at http://www,ahcpub.com. We look forward to hearing from you. ❖

In Future Issues:

Screening for Ovarian Cancer