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Chronic Lymphocytic Leukemia: Newly Recognized Molecular and Clinical Heterogenity

ABSTRACTS & COMMENTARY

Sources: Damle RN, et al. *Blood* 1999;94:1840-1847; Hamblin TJ, et al. *Blood* 1999;94:1848-1854.

Chronic lymphocytic leukemia (cll) is the most common leukemia in Western nations. About 14,000 cases are diagnosed each year in the United States. The disease usually has an indolent course until tumor cells replace and crowd out normal marrow elements. About 25% of patients develop some autoimmune disease in the course of their CLL and about half the deaths in patients with CLL are related to infection, to which patients have a heightened sensitivity because of a hypogammaglobulinemia as well as a decrease in host response to pathogens.

The malignant cell in CLL is a small lymphocyte with no obvious differences from normal lymphocytes, except perhaps a tendency to break up and smudge under the force generated by making a peripheral blood smear. The cell expresses surface immunoglobulin and other B-cell markers. Its most characteristic feature is the expression of CD5, a marker that is usually considered a T-cell marker. CD5+ B cells usually reside in the follicular mantle of lymph nodes and correspond to the B1 subset of cells in mice, which usually respond to foreign antigens without the help of T cells, do not generate immunologic memory, and do not carry mutations in their immunoglobulin genes (which means they have not passed through a follicle center to undergo immunoglobulin gene mutation). Most antibodies that recognize self antigens are generated by CD5+ B cells.

As laboratories have pursued the characterization of CLL cells in more detail, a certain heterogeneity has emerged that complicates the picture. However, reports from two leading groups studying CLL have used the heterogeneity to define at least two subsets of patients with CLL with significant differences in their natural history.

One group, Damle and colleagues, composed of researchers from North Shore Hospital (associated with New York University), Long Island Jewish Hospital (associated with Albert Einstein Medical Col-

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lege), and the University of Genoa, noted that patients differed in the degree of expression of CD38 (a cell surface marker) and the presence of mutations in their immunoglobulin genes. CD38 is a protein that has enzymatic activity; it converts nicotinamide adenine dinucleotide to cyclic adenosine diphosphoribose, a compound that binds to ryanodine receptors and regulates calcium flux.[1] In mice that have the CD38 gene knocked out, antibody responses to T-dependent antigens are greatly reduced.[2] CD38 is normally expressed on B cells that occupy the germinal center, where B cells go to mutate their immunoglobulin and generate antibody that has higher affinity for an antigen. Damle et al noted that about half of their 47 patients with CLL had tumor cells expressing immunoglobulin molecules that closely resembled the germline sequence and were not mutated; nearly all of these patients had CD38 expression on more than 30% of the tumor cells. By contrast, about half of the cases had tumor cells expressing immunoglobulin molecules that had undergone somatic mutation, probably in a germinal center; all of these patients expressed either no CD38 or only low levels of CD38. Cases with and without mutations were similar in all other surface markers, such as CD23, CD5, and CD19. Only CD38 expression was different between the groups.

When patient characteristics were examined, significant differences were found. In cases with mutated immunoglobulin genes and low CD38 expression, men and women were equally represented. By contrast, in cases with cells expressing germline immunoglobulin genes and high levels of CD38, males predominated. Differences were also found in response to therapy; those with unmutated immunoglobulin molecules and high CD38 expression responded poorly to chemotherapy whereas those with mutated immunoglobulin molecules and low CD38 expression were responsive to therapy. Most interestingly, patients differed in natural history based upon the status of their immunoglobulin genes. CD38-high unmutated immunoglobulin gene cases had a poorer median survival (9 years) than CD38-low mutated immunoglobulin gene cases (median survival not reached but exceeding 18 years). The Rai stage distribution is difficult to assess given the small number of patients. However, for those with intermediate Rai stage on clinical grounds, the two subtypes maintained significant survival differences—nine years for unmutated, and 17 years for mutated.

Hamblin and colleagues from the Royal Bournemouth Hospital and the Tenovus Research Laboratory performed a similar analysis of immunoglobulin gene mutations in CLL. They had previously shown that cases bearing unmutated immunoglobulin genes were more likely to harbor the trisomy 12 cytogenetic abnormality and have a poorer prognosis while those bearing mutated immunoglobulin genes more often had chromosome 13q 14 abnormalities and a better prognosis.[3] Hamblin et al analyzed 84 cases; around 45% had unmutated immunoglobulin genes and 55% had mutated immunoglobulin genes. Median survival for Binet stage A patients with unmutated immunoglobulin genes was about eight years; for those with mutated immunoglobulin genes, median survival was more than 24 years.

COMMENTARY

The conclusion that emerges from these seminal studies is that the clinical disease we call CLL is really at least two diseases. One disease is derived from a memory B cell that has passed through a germinal center, mutated its immunoglobulin gene in response to an antigen, and been transformed. This disease is associated with interstitial deletions in the retinoblastoma gene product, affects men and women equally, and has an extremely indolent natural history. When treatment is needed, it responds well to therapy. The other disease is derived from an antigen-naive B cell from the marginal zone of lymph nodes,

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has never passed through a germinal center, has not mutated its immunoglobulin genes, and is probably related to mantle zone lymphoma. This disease is associated with trisomy 12, affects men predominantly, and has a more aggressive natural history (median survival 8 years). This disease is more refractory to chemotherapy.

While no one is anticipating a sudden expansion of molecular immunology labs capable of analyzing tumor-associated immunoglobulin genes for the presence of somatic mutations as a component of a routine diagnostic clinical pathology laboratory, the Damle et al study suggests that a surrogate marker for immunoglobulin gene mutation is CD38 expression. CD38 expression is routinely measureable using a standard flow cytometer. Thus, one imagines that a CLL panel will emerge in the diagnostic laboratory in which cells are labeled with anti-IgM or anti-CD19 to identify them as B cells, with anti-CD5 to identify them as CLL B cells, and with anti-CD38 to separate the good (CD38 low) from the bad (CD38 high). It is possible that once this separation of subsets has occurred, other markers that have been reported to assess prognosis in CLL such as beta 2-microglobulin levels, soluble CD23 levels, or soluble deoxythymidine kinase levels would add further clinical information.[4-6] However, the question of the value of other markers needs to be addressed in a large study in which sufficient numbers of patients are analyzed and the two major subcategories of CLL are separated.

In my view, both studies overinterpret the data when they try to conclude that these differences make some sort of sense because the disease that gives rise to CLL with unmutated immunoglobulin genes is derived from a more primitive B cell than the disease that gives rise to CLL with mutated immunoglobulin genes. Disease natural history is determined by many factors and the level of differentiation of the normal cell that is transformed is one of the least reliable predictors of natural history. The most clinically aggressive lymphoid malignancy is Burkitt's lymphoma, which is a neoplasm of mature germinal center B cells, not a tumor derived from the most primitive lymphoid precursor. It is difficult for me to understand how this old canard keeps surviving peer review. In general, one can learn little about the natural history of a lymphoid neoplasm on the basis of knowing where in normal lymphoid differentiation the tumor arose.

What's next for CLL? Certainly these papers mark a point of departure in the history of the study of this disease. It is hoped that once the two newly defined subsets are recognized prospectively, it may be possible that study of the more aggressive, treatment-refractory form will yield clues to its management. For the favorable prognosis subset (CD38 low), we do not have curative therapy, but it isn't completely clear that we need it. Median survivals in excess of 24 years in a disease that mainly affects people older than the age of 60 do not lead one to prioritize its treatment as high as say breast, colon, lung, and prostate cancer. ❖

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Antibody to CD47: Preclinical Promise for Chronic Lymphocytic Leukemia

ABSTRACT & COMMENTARY

Synopsis: *The antibody against CD47 or the natural ligand for CD47, thrombospondin, was able to kill leukemic cells from 42 patients with chronic lymphocytic leukemia. This target may be suitable for clinical application.*

Source: Mateo V, et al. *Nat Med* 1999;5:1277-1284.

Chronic lymphocytic leukemia (cll) is one of the more common lymphoid malignancies. Treatment in the early stages of disease does not improve the prognosis.[1] When the disease becomes symptomatic, nucleosides, especially fludarabine, and alkylating agents such as chlorambucil are frequently capable of producing antitumor responses for variable periods. However, no curative therapy is available.

As more is learned about the biology of lymphoid cells and the tumors derived from them, it has become clear that certain signals that are involved in normal lymphocyte regulation may provide an effective means of treating tumors. Thus, there is now preclinical evidence that aggressive histology B-cell lymphomas may be killed by activating the CD40 molecule on their surface.[2] The CD30 molecule on the surface of anaplastic large cell lymphoma may be an effective target for therapy.[3] In addition, recent data on CLL cells have identified a potential target for biologic therapy in this form of lymphoid malignancy.

Thrombospondin is a major component of alpha granules in platelets and is produced by other cells as well. It is an adhesive glycoprotein that is produced by

platelets locally and appears to inhibit fibrinolysis; thus, it helps maintain clot integrity. However, many additional roles for the protein are being uncovered, including roles in angiogenesis and phagocytosis. One receptor for thrombospondin is CD47, also known as integrin-associated protein because it is often found in association with integrin molecules, especially alpha v beta 3, which is also known as the vitronectin receptor. On lymphoid cells, CD47 is expressed independently from integrins.

Mateo and colleagues examined the in vitro effect of CD47 ligation on the survival of CLL cells obtained from 42 different patients. Antibody to CD47 and thrombospondin itself were both used as ligands. Cells exposed to these stimuli adhered strongly to the plastic culture dish and began to undergo programmed cell death or apoptosis. However, unlike most forms of apoptosis, the cells died without activating the caspase pathway (caspases are proteases that destroy many key proteins necessary for damage repair). Among the cells dying from CD47 ligation were at least two cases in which the CLL cells were refractory to glucocorticoid-induced apoptosis, a finding often associated with refractoriness to treatment. Other stimuli, for example, antibody to CD5, can also induce the adherence of CLL cells to plastic, but this is not accompanied by the death of the cells. Thus, signal transduction through CD47 is thought to send a death signal to the cell and adhesion is not sufficient to send that signal. The death signal is strong; after 30 minutes of exposure, death was irreversible.

A number of factors have been identified that help CLL survive in vitro and presumably in vivo. These factors include interleukin-4 and interferon-gamma. Although both of these factors as well as adherence to bone marrow stroma protected CLL cells from spontaneous apoptosis in vitro, none of these factors could prevent CD47-induced apoptosis.

COMMENTARY

So what will it take to make thrombospondin, or anti-CD47 antibody, an effective treatment for CLL? The steps for clinical development are well-defined. But what are the odds that CD47 represents a useful therapeutic target? Several features of the effects of CD47 stimulation are encouraging. It seems to be working in a fashion that is distinct from drugs and glucocorticoids. The apoptosis induced by these agents is caspase-dependent whereas CD47-induced apoptosis is caspase-independent. It is possible that one mechanism of resistance to standard treatment involves the development of defects in the caspase pathway. Thus, CD47 activation may be effective in drug-resistant cases of CLL. Preliminary evidence suggests this is the case. Of the 42 cases examined by Mateo et al, several were resistant to drug-induced killing but all 42 showed dramatic killing by CD47 ligation. Furthermore, drug-induced killing can be largely reversed by interleukin-4 and interferon-gamma, agents that have no effect on CD47 killing.

Another intriguing feature of the CD47 effect is its speed and irreversibility. CD47 ligation induces signal transduction and the pathways that are activated through the receptor are still being defined. However, cell death signalling is one of the most promising areas of targeted drug development for cancer.

Arguing against CD47 as a therapeutic target are its widespread distribution, its poorly defined function, the widespread distribution of its natural ligand, the poorly defined function of its natural ligand. We have no idea of the range of normal cells that express CD47 or what would happen to them if they suddenly received a signal through it. Will there be a therapeutic index? Will the receptor down-modulate or shed from the cell surface? Will the cells develop resistance to CD47 signalling? Much is yet to be defined. However, it is at least encouraging that we now know enough about the cell biology of CLL cells that an alternative to DNA poisons can at least be tested for its therapeutic potential. ❖

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Sperm Cryopreservation and Recent Advances in Assisted Reproduction Techniques for Cancer Survivors

ABSTRACT & COMMENTARY

Synopsis: *A survey of oncologists in Minnesota examined knowledge and attitudes about sperm cryopreservation for male patients with newly diagnosed cancer. Enthusiasm for this undertaking was only moderate, related to lack of information about the technical advances and the improved fertility rates.*

Source: Zapzalka DM, et al. *Cancer* 1999;86: 1812-1817.

With steady improvements in cancer treatment, more patients are being cured of cancer and

have an expectation of normal or near normal life span. Many of the most curable malignancies occur in young people. Malignancies such as leukemia, lymphoma, and testicular cancer are not uncommon in young men. Perhaps because there always seems to be great urgency in starting therapy in newly diagnosed patients, issues of long-term family planning are frequently overlooked. For males, the procurement and cryopreservation of sperm can be done. However, the perception is that this is expensive, takes too much time because of the need for multiple donations, that the quality of sperm is often poor even before therapy (related to effects of the cancer), and that the success rate is quite low. I can recall thinking somewhat sardonically, we should be so lucky as to have this patient survive to experience childlessness.

Zapzalka and colleagues surveyed the current knowledge, opinions, and clinical practices of American Society of Clinical Oncology (ASCO) members in the state of Minnesota regarding pretherapy cryopreservation of semen. Forty-six of 165 oncologists (28%) responded to the written questionnaire. The responding oncologists did discuss cryopreservation with their patients, but their enthusiasm for the intervention was only moderate (mean 5.8 ± 2.2 on a scale of 1-10). They perceived the importance of the procedure to the patient to be somewhat greater (6.8 ± 2.5). The factors that were considered important in their recommendation were patient age, type of treatment, type of cancer, and the urgency for starting therapy. Included, but less commonly mentioned, were pre-existing infertility, number of children, marital status, and cost. A majority of respondents knew where patients could go to have sperm cryopreserved, but less than half gave accurate information about the costs of the procedure.

Zapzalka et al speculate that some of the lack of enthusiasm for referring patients for cryopreservation is based upon the assumption that the procedure is likely to be ineffective due to diminished sperm quality, even before chemotherapy, and to the lack of awareness of the recent advances in assisted reproductive techniques. They point out that in vitro fertilization has been greatly enhanced by new intracytoplamic injection techniques. Their survey would indicate that there is a need for re-educating medical oncologists on this topic.

COMMENTARY

Infertility is common in cured cancer patients. Whether this is the result of therapy or just associated with the underlying disease is not completely clear, and it is likely that both factors make a contribution. But the fact remains that fertility rates are low in this population.[1,2] Assisted reproductive technology has, in recent years, progressed to such an extent that in vitro fertilization using small quantities of male sperm has been successful in the majority of cases.[3] The technique of injecting single sperm directly into the egg cytoplasm has been a major breakthrough in this technology and men who once had little or no chance of producing a pregnancy through assisted techniques now have fertility rates approaching that of couples undergoing standard in vitro fertilization in whom male infertility is not involved.

The data from this survey would indicate that oncologists are not aware of these advances. Of course, this was a small survey with about 25% of respondents from a single state. Yet, the responders, if anything, were probably more likely to be aware or sensitive to the issues presented and, still, it appears that there is both misinformation and lack of awareness of recent advances. Possibly this is a regional phenomenon due to local cultural or practice patterns, a caveat not mentioned by Zapzalka et al, but this seems unlikely. More likely is that currently practicing medical oncologists have yet to witness or learn about these advances and, thus, maintain an attitude toward sperm cryopreservation based upon prior disappointments. If, indeed, these advances are as successful as reported, oncologists may be doing a disservice to those selected patients in whom post-therapy family planning will become an issue by foregoing a discussion and facilitation of semen collection and cryopreservation before therapy. ❖

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Quality-of-Life is Better for Older Patients With Early Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *In this study, women with early stage disease completed a questionnaire that included measures of quality-of-life and depression. Approximately half of the patients were younger than 50 years of age and half older than 50 years of age.*

Source: Wenzel LB, et al. *Cancer* 1999;86:1768-1774.

Quality-of-life was compared in younger vs. older women with breast cancer just after completion of therapy for early breast cancer. The data were derived from the initial interviews with breast carcinoma patients

that had enrolled in a clinical trial of psychosocial telephone counseling.[1] The current assessment was made by written questionnaire, which included standardized measures of quality-of-life including the Functional Assessment of Cancer Therapy-Breast instrument (FACT-B), the Center for Epidemiologic Studies of Depression Scale (CES-D), and the Impact of Event Scale.[2-4]

Of 354 patients invited to participate, 304 (86%) agreed and completed the questionnaires. Fifty-three percent were younger than 50 years of age. The demographic profile indicated that most of the women were white, educated, married, and employed outside of the home. The older women (age > 50) were similar, except they were less likely to have received a college education and be employed full time, but were more likely to report additional chronic health problems and be widowed.

The majority of patients enrolled had early stage disease (tumor classified as T2 or less and no positive lymph nodes). However, there were rather striking treatment differences, with the younger patients more likely to have received chemotherapy and the older patients more likely to have received tamoxifen. There was no significant difference in the type of surgery (lumpectomy vs mastectomy), yet younger women were more likely to receive immediate reconstruction.

The FACT-B quality-of-life instrument revealed a significantly better quality-of life for the older patients, particularly with regard to the measures of emotional well-being and certain breast cancer specific items. Furthermore, no significant age-specific differences emerged with respect to sexual functioning and body image.

Similarly, there were age-related differences in "clinical levels" of distress. Younger women were more likely to experience depressive symptoms and breast carcinoma-specific intrusive and avoidant thoughts, with scores on the CES-D indicating a significant number experiencing levels of distress of clinical importance. For example, 32% of younger patients experienced depressive symptoms in the clinically important range (CES-D scores > 16) compared to 20% of patients older than 50 years of age (P = 0.041). The scores for the younger patients suggested that they exhibited depressive symptoms to a greater extent than normal for that age population. The older patients did not appear to be more depressed than similarly aged women without breast cancer.

COMMENTARY

This report confirms what many practitioners would have predicted, older women are less devastated by a diagnosis of breast cancer. In this study, all of the women had early stage disease and had just completed initial therapy. The younger women were more likely to have received chemotherapy and the older women hormonal therapy. This fact alone could explain some of the observed differences. Fatigue, malaise, nausea, the common chemotherapy side effects most certainly would contribute to impaired quality-of-life and depression, especially immediately after treatment, which was when this study was conducted. However, whatever the cause, it is hard to refute the conclusion of Wenzel and colleagues that younger women with breast cancer are at high risk to have adversely affected quality-of-life and depression. Accordingly, this age cohort might be preferentially selected for targeted interventions, such as the counseling program that is now being investigated.

The question of the influence of age on the development of cancer-related disruption of quality-of-life and depression cannot be fully addressed by the current study, primarily because of the treatment differences noted. Furthermore, the disease might be different in younger patients, and this itself might influence these developments. Older women are more likely to have less aggressive tumors, fewer negative prognostic factors, greater hormone receptor expression, etc., and this may influence well-being in ways that we are unable to define.[5]

A study designed to address the influence of age (independent of chemotherapy and tumor characteristics) would have to control for all of these factors—and that would be a monumental undertaking. If one were to design such a study, from a gerontological perspective, more disparate age groups should be identified. It would be interesting to compare women older than 70 years of age (close to the majority of breast cancer patients) with those who are clearly premenopausal (< 40 years of age at presentation) and those in the intermediate ages (41-55 and 56-69 years of age).

It is unlikely that such a study could or would be done. Yet, from a practical point of view, we can accept the current findings, and resist the temptation to overinterpret them. Young women with breast cancer are more likely to sustain a negative psychological effect, and this should be taken into consideration, both by attending physicians and staff, and by those intending to investigate new psychological and social interventions. ❖

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Is it Time to Transfer Flexible Sigmoidoscopy to Non-Physician Endoscopists?

ABSTRACTS & COMMENTARY

Synopsis: *In this report, a large series of patients were examined by either an experienced gastroenterologist or a trained, nonphysician endoscopist. The outcomes were nearly identical, no complications occurred, and the costs of the procedure were approximately $100 less if performed by the nonphysician endoscopist.*

Sources: Wallace MB, et al. *Am J Med* 1999;107: 214-218; Shaheen NJ, Ransohoff DF. *Am J Med* 1999;107:286-287.

Routine screening of individuals older than 50 years of age by flexible sigmoidoscopy has been shown to be an effective way to reduce mortality from colorectal cancer.[1,2] Yet, only a small percentage of patients are screened.[3] Although there are a number of reasons for this failure to screen, one is the limited supply of trained endoscopists. To meet this need, it has been proposed that trained, nonphysician endoscopists perform routine examinations. In the current report, Wallace and colleagues from the Division of Gastroenterology at Brigham and Women's Hospital, Harvard Medical School, describe their experience with nonphysician endoscopists.

Asymptomatic patients 50 years of age or older without evidence for intestinal blood loss or symptoms and without a personal or family history of colon cancer were examined by flexible sigmoidoscopy performed either by a staff gastroenterologist or nonphysician endoscopist. There were 15 gastroenterologists and three nonphysician endoscopists (1 nurse practitioner and 2 physician assistants) that participated in the program. Outcomes included the depth of examination, number and histology of polyps, and complications.

Nonphysicians performed 2323 sigmoidoscopy examinations, and physicians performed 1378 examinations. Depth of exam was no different between the groups (52 ± 10 cm for exams by the nonphysicians and 55 ± 9 cm for exams by the gastroenterologists). Similarly, there was no difference in the number of polyps observed or biopsied. No major complications occurred in any of the exams. The cost per examination, including the nonphysician training cost, was lower for nonphysicians ($186) than for physicians ($283).

Wallace et al conclude that appropriately trained nonphysicians are capable of performing safe and effective screening for colorectal cancer by flexible sigmoidoscopy. Recruitment of such individuals may improve availability and reduce the cost of the procedure.

COMMENTARY

There are a number of reasons why the majority of individuals who might benefit from screening sigmoidoscopy don't undertake the procedure. There is the perception that the procedure is both uncomfortable and embarrassing.[4] Furthermore, there is the issue of availability. In general, primary care physicians have been slow to pick up the technique for a number of reasons including the training time involved, the cost of equipment, including maintenance, and the low rate of reimbursement from Medicare or other insurance carriers. Shaheen and Ransohoff emphasize this latter point in the commentary accompanying this report. They note that Medicare reimbursement for the procedure without biopsy is $86.76, well below the costs for either physician or nonphysician endoscopists from the Harvard group. The derivation of the costs involved is complicated, and not satisfactorily established. Yet, there is no question that the costs are lower with the nonphysician endoscopists. In the current study, the approximate $100 difference was the result of salary costs alone. However, even with this savings, the costs exceed the current reimbursement rate by a substantial margin. Physicians might well be ready to transfer the procedure to nonphysician endoscopists on this basis alone.

However, the issue of examination quality remains, and was directly addressed in this report. The three nonphysician endoscopists were well-trained and quickly developed substantial experience with the technique. Upon analysis, there was no difference in examination performance or outcome. However, Wallace et al did not comment on patient satisfaction and this may be a factor in some communities. Furthermore, although there were no complications in this series, some are bound to occur in time (with either a physician or nonphysician endoscopist) and one can envision a great potential for liability if a complication occurred during a procedure performed by a nonphysician. Yet, like a number of other clinical tasks once solely in the domain of physicians, it is likely that routine flexible sigmoidoscopy will soon be handed off to nonphysician endoscopists who, after suitable (and hopefully, standardized) training, can perform

the procedure efficiently and in high volume. This will then reduce costs and make available an effective screening procedure for a large population of individuals, some of whom will be discovered to have surgically curable colorectal cancer. ❖

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CME Questions

17. Which of the following statements about quality-of-life in patients with early stage breast cancer can be stated with confidence based on the evidence?

a. Younger patients are more likely to sustain disruption of their quality-of-life when compared to older women.
b. Older patients have poorer quality-of-life than younger patients, but have less impairment created by cancer therapy.
c. Younger patients have poorer quality-of-life than older patients, but the effect is clearly due to the fact that they are more likely to receive chemotherapy.
d. Cancer therapy influences quality-of-life in a negative way but there is no age difference (younger patient vs older patient) in this negative effect.
e. Older patients have more treatment-related toxicity than younger patients.

18. Which of the following statements about referring patients for sperm cryopreservation is *true*?

a. It should be reserved for patients who have normal, pretherapy sperm counts as in vitro techniques for fertilization are unsuccessful with less than optimal sperm.
b. In vitro fertilization is unlikely to be successful in just about all cases and, thus, cryopreservation of sperm is not likely to be of value.
c. New technical advances have made in vitro fertilization much more successful and patients should be made aware that sperm cryopreservation is an option to allow later pregnancies.
d. Several semen collections will be necessary because the new techniques for in vitro fertilization require large numbers of sperm.
e. It should not be offered because most men with cancer have defective sperm.

19. Chronic lymphocytic leukemia now appears to be at least two distinct diseases based on what features?

a. Clinical stage and serum-soluble CD23 levels
b. Clinical stage and serum beta-2-microglobulin levels
c. CD38 and CD5 expression on the tumor cells
d. CD38 expression and immunoglobulin gene mutations in tumor cells
e. CD5 expression and trisomy 12

20. Chronic lymphocytic leukemia cells can be killed in vitro by exposure to which of the following agents?

a. Thrombomodulin
b. Thrombospondin
c. Thrombopoietin
d. Thromboglobulin
e. Fibronectin

21. Which of the following statements about colorectal cancer screening by flexible sigmoidoscopy is *not* true?

a. The procedure is an effective screening tool for the discovery of surgically curable cancers.
b. The procedure can be performed safely and effectively by nonphysician endoscopists.
c. The procedure can be performed safely by nonphysicians, but the outcomes are not as optimal as if the procedure were performed by a gastroenterologist.
d. The costs of the procedure can be substantially reduced if pe formed by a nonphysician endoscopist.
e. Flexible sigmoidoscopy performed by either physicians or no physicians is effective in detecting curable colon cancers.

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. You can also reach the editors and customer service personnel for *Clinical Oncology Alert* via the Internet by sending e-mail to holland.johnson@medec.com. ❖

Note to our Readers

American Health Consultants would like to thank Dr. Dan Longo for his 14 years of expertise, dedication, and hard work as editor-in-chief of *Clinical Oncology Alert*. This is Dr. Longo's final issue. With the January 2000 issue, Dr. William B. Ershler will begin serving as editor-in-chief. The Director at the Institute for Advanced Studies in Aging and Geriatric Medicine in Washington, D.C., Dr. Ershler's enthusiasm will help *Clinical Oncology Alert* continue to be the leading newsletter in oncology. ❖

In Future Issues:

New Editor for Clinical Oncology Alert