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Histologic Progression of Follicular Lymphoma: Efficacy of High-Dose Therapy and Autologous Bone Marrow Transplant

ABSTRACT & COMMENTARY

Source: Friedberg JW, et al. *Biol Blood Marrow Transplant* 1999:5;262.

About 20-25% of all lymphomas are follicular lymphomas and the majority of these cancers present with disseminated disease. As they are derived from follicular center B cells, they have a tendency to undergo mutations in their immunoglobulin genes, and increasingly it appears that this genetic instability affects other genes as well. Follicular lymphoma may remain indolent in its clinical growth for a number of years, but up to 90% of patients dying with a diagnosis of follicular lymphoma have experienced histologic transformation from a follicular pattern of growth to a diffuse pattern of growth.[1]

And when the pattern of growth changes, so too does the natural history.[2,3] Patients with histologic transformation of follicular lymphoma to diffuse large B-cell lymphoma have a median survival of 6-8 months.[4]

Efforts to treat transformed diffuse large-cell lymphoma in a fashion similar to de novo diffuse large-cell lymphoma have generally found that some patients may achieve durable remissions, but the frequency of successful treatment is lower with transformed than with de novo patients. Recently, Friedberg and colleagues from the Dana-Farber Cancer Institute reported on the use of high-dose therapy and autologous bone marrow transplantation in 27 patients with transformed lymphoma.

Twenty-one of the reported patients had an original diagnosis of follicular lymphoma and six had Richter's transformation from chronic lymphocytic leukemia. Age ranged from 29 to 58 years, median 44 years. Median time of histologic transformation from diagnosis was three years (range, 6 months-15 years). All patients received conventional dose therapy to reduce tumor bulk to lymph node masses less than 2 cm and bone marrow involvement of less

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than 20% of the marrow space. The preparative regimen was cyclophosphamide (60 mg/kg) given daily twice followed by three days of hyperfractioned total body radiation therapy.

There were no acute treatment-related deaths, although four patients developed secondary myelodysplasia or acute leukemia and three of these patients died. Twelve patients (44%) are alive and free of disease a median of three years after treatment. Eleven patients (41%) experienced disease progression after treatment and nine of these patients have died.

Outcome was analyzed for the influence of a variety of prognostic factors. Interestingly, patients who had undergone histologic transformation within 18 months of diagnosis had a significantly better treatment outcome than those who had a longer period of indolent lymphoma before progression. Five-year disease-free survival was 62% for early transformers compared to 31% for those whose transformation occurred more than 18 months after diagnosis. Overall survival at five years was 80% for the early transformers and 31% for the late transformers.

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COMMENTARY

Histologic transformation of follicular lymphoma appears to occur as a consequence of accumulation of genetic damage. The new tumor is a genetically altered version of the original tumor in the vast majority of cases.

New cytogenetic lesions affecting chromosomes 6p, 17p, and 9p are particularly common after histologic transformation and alterations in the function of the p53 gene on chromosome 17p and the cyclin-dependent kinase inhibitors, p15 and p16 on chromosome 9p are thought to be involved in the accelerated growth.[5-7] It is unclear how these tumors differ in molecular terms from the de novo diffuse large B-cell lymphomas that they resemble microscopically; however, whatever the differences, the result appears to be a greater likelihood of drug resistance.

The results reported by Friedberg et al suggest that perhaps as many as half of the patients who undergo histologic transformation from an indolent to a diffuse aggressive lymphoma are curable with high-dose therapy and autologous bone marrow transplantation. This fraction is similar to the fraction of patients with relapsed diffuse large cell lymphoma that may be curable by this modality. The extremely poor outcome from the use of CHOP in patients with histologic transformation combined with the relatively greater success of the high-dose therapy approach makes it reasonable to consider high-dose therapy approaches as the treatment of choice in patients with histologic transformation.

The apparent influence of time to transformation on treatment outcome in this study is a surprise. Friedberg et al attempted to ascertain if there were significant differences in the amount of prior therapy given to the early vs. the late transformers. However, this variable did not appear to explain the observed differences. It would be of enormous interest to compare the genetic lesions in early vs. late transformers to try to better understand if there are molecular predictors of response to therapy in this setting. ❖

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Developing a Treatment Strategy Based Upon Risk Factors for Patients With High-Grade Lymphoma

ABSTRACT & COMMENTARY

Synopsis: *The treatment outcome of patients with intermediate- or high-grade lymphoma with three poor prognostic factors remains unsatisfactory. In this study from a single institution within the United Kingdom, patients with poor-risk, high-grade lymphomas were treated initially with conventional chemotherapy followed by high-dose chemotherapy and peripheral blood stem cell rescue. An overall 64% complete remission rate was achieved. Prognostic factors that were associated with poorer outcome included bulky mediastinal mass, more than three extranodal sites, and low-serum albumin. Interestingly, remission status before HDCT PBSC was not found to influence event-free survival or overall survival, suggesting that early introduction of HDCT may be of benefit to those patients in partial remission.*

Source: Lee SM, et al. *Bone Marrow Transplant* 1999; 24:271-277.

Treatment for diffuse aggressive lymphomas remains a challenge. Lee and associates at Christie Hospital (Manchester, UK) designed a study to identify the factors that convey the highest risk for treatment failure in patients with high-grade non-Hodgkin's lymphoma. Sixty-six patients with intermediate- or high-grade lymphomas and two or three adverse prognostic factors as defined by the age-adjusted International Prognostic Index (IPI) received induction treatment with 7-11 weeks of doxorubicin, cyclophosphamide, vincristine, bleomycin, etoposide, prednisolone, and methotrexate (VAPEC-B) followed by three cycles of ifosfamide/cytarabine (a subgroup of these patients with Burkitt's and lymphoblastic lymphoma had VAPEC-B followed by three cycles of high-dose methotrexate).[1] Subsequently, all patients received high-dose chemotherapy (HDCT) with busulphan/cyclophosphamide followed by autologous peripheral blood stem cell (PBSC) rescue.

Of the 66 patients treated, 47% achieved complete remission (CR) before the high-dose phase of the treatment regimen. All but one of the remaining had achieved a partial remission (PR) before HDCT. Following the HDCT, 64% were in CR and 19% had a PR. One patient had progressive disease and four patients died of treatment-related toxicity. For survivors (n = 46), at a median follow-up of 27 months, the actuarial three-year estimate of overall survival was 67%, event-free survival was 65%, and freedom from progression was 70%.

Examining this series by univariate analysis of risk factors, reduced survival was associated with mediastinal bulk, more than three extranodal sites, remission status before HDCT, low-serum albumin, and elevated erythrocyte sedimentation rate. No significant difference was observed between patients with intermediate- or high- grade histology or between patients with two or three IPI-defined adverse factors. When subjected to multivariate analysis, mediastinal mass, more than three extranodal sites and low-serum albumin persisted as independent predictors of survival but remission status before HDCT was not found to be significantly associated with poor outcome.

Based upon these three adverse factors (mediastinal bulk, > 3 extranodal sites, and low-serum albumin) the data were reexamined and patients were identified in one of three groups (0, 1, or > 2 adverse prognostic factors) and these were found to have significantly different outcomes. Event-free survival was 85% for the low-risk group, 63% for the intermediate-risk group, and 29% for the high-risk group. Overall survival was 84% for the low-risk group, 64% for the intermediate-risk group, and 25% for the high-risk group.

Lee et al suggest that those patients with intermediate- or high-grade lymphomas and two or more of these particular adverse prognostic factors do not respond well to conventional dose therapy followed by HDCT and PBSC rescue, and that these individuals should be considered for alternative (experimental) approaches from the outset.

COMMENTARY

Clinicians treating lymphoma have long been aware of the myriad of adverse clinical prognostic factors that are independent of specific histology and stage. This report reemphasizes their potential importance in establishing prognosis for patients with intermediate- or high-grade lymphoma and raises the suggestion that those with two or more of the adverse factors identified here (which differ from the IPI factors) be considered for alternative therapies. This, of course, would be reasonable if potentially more effective therapies were available. However, one poor-risk patient in four is a long-term disease-free survivor with this therapy and it seems unreasonable to me to pass up even that small potential for cure to try untested approaches, unless they included therapy at least as intense as VAPEC-B

plus HDCT and PBSC.

One intriguing point emerging on multivariate analysis in the current series is that partial remission to conventional-dose chemotherapy before HDCT and PBSC rescue was not found to be associated with poorer outcome than that seen in those who had achieved complete remission to conventional-dose therapy. In most other series, PR after conventional chemotherapy for patients with high-grade lymphomas has been associated with poor outcome (for example see[1]). This might imply that there are differences in the ability of HDCT to rescue partial responders treated with CHOP vs. partial responders treated with VAPEC-B. Alternatively, the particular preparative regimen used at Christie Hospital may be more effective than other such regimens. It is also important to distinguish results obtained at a single institution from results generated in a cooperative group. Often cooperative groups obtain poorer results, though this is not universal (results from the French GELA group are among the best in the world). While some interpret these differences as reflecting the inclusion of patients with poorer prognosis on group studies, careful analysis of results of technically demanding treatments such as HDCT and PBCS demonstrate that experience influences the outcome. Centers that use HDCT in fewer than six patients per year have a poorer outcome than those with more experience do.

As noted above, the prognostic factors defined in this series differ from those found in the IPI. The IPI did not examine serum albumin. However, in the IPI, more than one extranodal site conferred a poor prognosis while, in the Christie Hospital series, three or more extranodal sites were indicative of a poor prognosis. Of course, the IPI project involved many more patients. However, it may be of importance to note that most of the patients from whom the IPI was derived were treated with CHOP. If a therapy came along that was more effective than CHOP, one might expect that the prognostic factors would change. In this instance, more aggressive treatment appears to have shifted the threshold for extranodal sites. It takes three or more to influence prognosis when VAPEC-B and HDCT and PBSC are used as treatment, not more than one, as observed with CHOP.

Despite the notable results from this and other series, the use of HDCT and PBSC rescue for high-grade lymphomas remains controversial.[2-6] There have been recent reports indicating improved remission rates and overall survival using this approach. However, convincing randomized trial results have not been obtained. Several large scale, multi-institutional trials are ongoing. It would be ideal if patients with poor prognostic factors could be entered into one of these studies. ❖

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Interferon Treatment for Hepatitis C Prevents Hepatocellular Cancer

ABSTRACT & COMMENTARY

Synopsis: *In a large, retrospective series of hepatitis C patients, most of whom were treated with interferon, factors associated with hepatocellular cancer development were examined. Patients with pretreatment mild to moderated fibrosis, but without cirrhosis, had the greatest benefit from interferon treatment. Those with cirrhosis or high serum transaminase levels before treatment did not achieve significant benefit and the development of hepatocellular cancer was not different from those who were untreated.*

Source: Yoshida H, et al. *Ann Intern Med* 1999;131: 174-181.

Hepatitis c has become recognized as a major worldwide epidemic.[1] One consequence of chronic hepatitis C infection is hepatocellular carcinoma, but for some, this outcome can be avoided by interferon therapy.[2,3] It is not clear which patients benefit from this preventive measure. Thus, in a multi-institutional study within Japan, 2890 patients with chronic hepatitis C were analyzed retrospectively with regard to risk factors, interferon treatment, and cancer development.

Of the 2890 patients with hepatitis C and liver biopsies, 2400 were treated with interferon and 490 were untreated. The liver biopsies were all obtained before treatment and the degree of fibrosis was scored from F0 (no fibrosis) to F4 (cirrhosis). Response to interferon was determined virologically (hepatitis C virus RNA by RT-PCR) and biochemically (serum alanine aminotrasferase, ALT). Screening for development of hepatocellular carcinoma was performed periodically during an average follow-up of 4.3 years.

Hepatocellular carcinoma developed in 89 interferon-treated patients (1.1%) and in 59 (3.2%) untreated

patients. Among the untreated patients, the annual incidence of hepatocellular carcinoma increased with the degree of liver fibrosis, from 0.5% among patients with stage F0 or F1 fibrosis to 7.9% among patients with F4 fibrosis (cirrhosis). The cumulative incidence in treated and untreated patients differed significantly for patients with F2 fibrosis (P = 0.0128) and for those with stage F3 fibrosis (P = 0.0011). Incidence in F4 patients was not affected by interferon treatment. In multivariate analysis, interferon therapy was associated with a reduced risk for hepatocellular carcinoma, especially among patients with sustained virological response, persistently normal ALT levels, or ALT levels less than two times the upper limit of normal.

Thus, Yoshida and associates conclude that their data demonstrate interferon significantly reduces the risk of hepatocellular carcinoma, especially among those who are shown to respond to treatment by improved viral load and biochemical markers.

COMMENTARY

This is a retrospective analysis with a few methodological concerns. Treatment and nontreatment groups were not randomly assigned. Details of the interferon treatment were not provided, except to note that a certain percentage (most) received interferon alpha, others received interferon beta, and still others received both. Treatment schedules, modifications, and toxicities were not detailed. More importantly, explanations for why the 490 individuals were (or chose to be) untreated were not included and this leads to the possible interpretation that other factors existed that would alter the risk for cancer development (e.g., alcohol use, etc.). Nonetheless, as Yoshida et al indicate, these days it would be difficult to do a randomized trial of interferon treatment with published clinical trials already indicating some level of efficacy.

The paper does provide useful, new information. Patients with hepatitis C and existing cirrhosis were shown to have a high incidence of hepatocellular carcinoma (annual incidence approaching 8%). These individuals did not have significant reduction in cancer development with interferon therapy, although there was a trend in that direction. Those patients with mild to moderate fibrosis were clearly benefitted by treatment whereas those without evidence of fibrosis had such a low incidence of hepatocellular cancer even when untreated that it was impossible to detect a treatment benefit.

As is the case with cancer treatment in which patients responding to chemotherapy can often be shown to have a survival advantage, hepatitis C patients who respond to interferon (by reduced viral load or biochemical markers) are also the ones who appear to benefit in terms of reduced cancer development. In this regard, the series provides some useful guidelines. Treatment-induced sustained clearance of virus (> 6 months), which was achieved in about one-third of patients, is a strong indicator of protection from cancer development, at least for the short-term (the median duration of follow-up in this report was only 4.3 years). Furthermore, serum ALT may prove as good a prognostic indicator as liver biopsy. The ALT levels correlated well with the absence or presence of persistent virus. The multivariate analysis revealed that the risk for hepatocellular cancer was reduced in patients with mildly elevated ALT levels (< 2 times the normal limit) by interferon treatment, but for those with ALT levels greater than twice the normal, there was no demonstrable benefit from interferon therapy. Accordingly, it should be noted that 70% of the interferon-treated patients in this series had high levels of ALT (> 2 normal) before treatment but this number decreased significantly (to 31%) after treatment.

Thus, data from this series add strength to prior reports that interferon treatment will prevent (or delay) the development of hepatocellular cancer in patients with hepatitis C. The patients who seem to benefit the most are those with mild to moderate fibrosis (F2 or F3) and pretreatment serum ALT levels that are less than two times the normal level. ❖

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Continuous Infusions of Doxorubicin and Paclitaxel in Refractory Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *Some tumors that are resistant to drugs administered by intravenous bolus may be sensitive to prolonged exposure achieved through continuous infusion.*

Source: Duska LR, et al. *Clin Cancer Res* 1999;5: 1299-1305.

Ovarian cancer is responsive to paclitaxel-containing chemotherapy programs, but only about

20% of patients are cured. Eighty percent relapse after a partial or complete remission or progress during primary treatment. Patients with primary progressive ovarian cancer are usually refractory to salvage therapy. Patients who relapse from a remission may be responsive transiently to a variety of agents including carboplatin, etoposide, topotecan, ifosfamide, or liposomal doxorubicin. However, curative salvage therapy does not exist.

Clinical studies in breast cancer have suggested that women who progress after primary therapy that includes paclitaxel may, nevertheless, respond to re-exposure to paclitaxel when it is given by continuous infusion.[1] Doxorubicin is not frequently used in primary therapy of ovarian cancer, but the activity of the liposomal preparation and the interaction between doxorubicin and paclitaxel in other tumor types led Duska and colleagues to do a phase I study of four-day infusions of doxorubicin and paclitaxel in women with relapsed ovarian cancer.

The dose of paclitaxel was held constant at 25 mg/m^2/d and the dose of doxorubicin was escalated in 2.5 mg/m^2/d increments from 7.5 mg/m^2/d to 15 mg/m^2/d. Blood counts were supported with granulocyte colony-stimulating factor 5 mcg/kg/d. Fifteen patients with documented progressive disease following primary treatment were entered into the study. Dose-limiting toxicity was hematologic. The maximum tolerated dose of doxorubicin was 12.5 mg/m^2/d. Nonhematologic toxicity was minimal. In particular, no cardiovascular complications were noted. Five of the 15 evaluable patients responded, four with partial responses and one with a complete response. At the maximum tolerated dose, no patients required dose modification or treatment delays.

Four-day infusions of paclitaxel and doxorubicin are active and well-tolerated in patients with relapsed ovarian cancer. Additional studies will define the response rate and duration in larger numbers of patients.

COMMENTARY

These results certainly seem promising. There has been remarkably little to cheer about in the salvage therapy of women with relapsed ovarian cancer. Continuous infusions are relatively easy to manage in patients with indwelling central-venous catheters and the side effects of this particular combination are sufficiently minor that outpatient therapy should be routine rather than the exception. It has been recognized that the administration of paclitaxel along with doxorubicin can slow doxorubicin clearance, an effect that appears to be attributable to the cremaphor vehicle in which the paclitaxel is formulated.[2] However, when paclitaxel is administered by slow continuous infusion, it is possible that the serum concentration of cremaphor does not reach the levels necessary to interfere with doxorubicin clearance. Certainly the pharmacokinetic data collected in this study did not suggest that the doxorubicin half-life was dramatically altered. It may be interesting to examine whether liposomal doxorubicin may have an even more impressive therapeutic index when combined with paclitaxel infusion. ❖

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Does Virtual Colonoscopy Make Fiscal Sense?

ABSTRACT & COMMENTARY

Synopsis: *Virtual colonoscopy refers to the newly developed imaging techniques using either computerized tomography or magnetic resonance, rapidly generated images to simulate colonoscopy. The technique has proven effective at detecting small colonic lesions and is safe and well-accepted by patients. In this report, a hypothetical population is used to calculate and compare (vs colonoscopy) the cost-effectiveness of this new technique as an initial screening tool for colorectal cancer. The data indicate that CT-colonography would be somewhat more expensive. It is suggested that, from a cost perspective, in order for it to replace colonoscopy as an initial screen, the procedural expenses would need to be reduced to a level 54% less than colonoscopy.*

Source: Sonnenberg A, et al. *Am J Gastroenterol* 1999; 94:2268-2274.

Computed tomography (ct) or magnetic resonance (MR) colonography is a novel application of computerized imaging designed to generate three-dimensional representations of the colon. Some have suggested that the technique be applied to widespread screening for colorectal cancer.[1,2] Both CT and MR techniques are reported to have high sensitivity (> 75%) and specificity (> 90%) in detecting colorectal cancer and polyps more than 10 mm in size.[3-5] However, the question remains whether there is added value to this approach when compared to colonoscopy alone.

In this report, the issues of cost-effectiveness were raised and a model was developed to assess the cost of this procedure compared to colonoscopy or no screen-

ing. A hypothetical population of 100,000 individuals aged 50 years undergoing screening every 10 years was used. Suspicious lesions picked up by the CT technique were further worked up by colonoscopy. For those requiring polypectomy, colonoscopy was repeated every three years until no adenomatous polyps were found.

The technique involves the generation of endoluminal images at a fast rate (15-30/sec). Subjects receive the same type of bowel cleansing as with colonoscopy and the colon is insufflated with 2 L CO_2 or room air. (For MR colonography, after the bowel cleansing the patient is given a single contrast enema of 2 L water containing 20 mL of gadolinium-DTPA). While a single breath is held, the subject is moved through a rotating x-ray beam of a helical CT scanner. With the rapid image generation, there is an illusion of traveling through the colon. The technique is reported to have a sensitivity of more than 75% and specificity more than 90% for detecting colorectal polyps or cancers of 10 mm size.[3-5] If polyps or other abnormalities are observed, conventional colonoscopy is required for further evaluation, biopsy, and/or resection.

Applying the Markov technique for cost effective modeling,[6] screening CT colonography costs $24,586 per life-year saved, compared with $20,930 spent on colonoscopy screening. The incremental cost-effectiveness ratios comparing CT colonography to no screening was $11,484, but comparing colonoscopy to CT colonography was $10,408. Thus, screening by colonoscopy is more cost effective. For the two procedures to become comparable, CT colonography needs to be associated with an initial compliance rate 15-20% better than colonoscopy or the procedural costs need to be more than 50% less than colonoscopy.

COMMENTARY

CT colonography has been advanced as a screening tool on the rationale that it will be well tolerated by patients, and be safe and effective at detecting small lesions.[3,4] However, the technique is still under development and it is not clear that these issues alone warrant replacing conventional colonoscopy screening. It is likely that it will be better accepted by patients than colonoscopy but the procedure still calls for bowel cleansing and gas insufflation, which are the most unpleasant features of colonoscopy for many patients. No anesthesia is involved and theoretically this provides a safety advantage. Reported levels of detection are excellent but these have come from the centers that developed the technique. No doubt, there is a learning curve and it would seem the gold standard for sensitivity and specificity would remain colonoscopy.

For screening techniques to be widely applied, they must also prove to be fiscally feasible. Thus, the current study using the Markov model for determining cost effectiveness is justified. An estimate from a typical population for whom screening by colonoscopy has proven both effective and cost effective provides a useful comparison. When examined by this model, it turns out that the new technique, when applied as initial screening, adds significant expense. Yet, it still falls within a level that would be considered reasonable. For example, the estimate is similar to the cost per year-of-life saved by mammography in the 50-69 year-old age group ($21,400) and is four times less expensive than similar estimates for mammography, if the 40-49 year-old age group is included ($110,000).[7,8]

Thus, the question remains whether this new technique should replace conventional colonoscopy as an initial screen for colorectal cancer. Perhaps the debate that is likely to develop will stimulate new advances in technique and, perhaps, reduced procedural costs (of 1 or the other) that will allow a clear choice. For now, and until more experience is gained, in most communities conventional colonoscopy remains the standard. ❖

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Are We Close to Curative Therapy for Colorectal Cancer Spread to the Liver?

ABSTRACT & COMMENTARY

Synopsis: *Giacchetti and colleagues have attempted to increase the fraction of patients with resectable metastases by delivering neoadjuvant chemotherapy to 151 patients with unresectable hepatic metastases.*

Source: Giacchetti S, et al. *Ann Oncol* 1999;10:663-669.

A small number of patients with colorectal cancer involving the liver have been curable by

surgical resection of limited numbers of lesions localized to one hepatic lobe. Giacchetti et al have attempted to increase the fraction of patients with resectable metastases by delivering neoadjuvant chemotherapy to 151 patients with unresectable hepatic metastases. Patients received 5-fluorouracil, leucovorin, and oxaliplatin as outpatients. Patients were intermittently reassessed for their eligibility for surgical resection.

The size of liver metastases decreased by more than 50% in 89 patients (59%). Median overall survival was two years, and 28% of the 151 patients were alive at five years. Surgery with curative intent was undertaken in 77 patients (51%) and complete resection was achieved in 58 patients (38% of the total, 75% of those undergoing surgery). The median survival of the patients who were operated on was 48 months.

COMMENTARY

These results appear almost too good to be true. In an accompanying editorial, it is revealed that much depends on the initial assessment that the liver lesions were unresectable. If a substantial fraction of the patients had resectable metastases before the neoadjuvant chemotherapy, the results would appear somewhat less impressive. However, it is unlikely that a substantial fraction of these patients were misclassified. Perhaps the addition of oxaliplatin to 5-fluorouracil and leucovorin will make a difference in the frequency and magnitude of the responses in colorectal cancer. Efforts to replicate and expand these findings should have a high priority. ❖

CME Questions

9. Which of the following statements about applying CT colonography as an initial screening tool for colorectal cancer is *true*?

a. In terms of costs per year-of-life saved, it is less expensive than when colonoscopy is the initial screening tool but the sensitivity of colonoscopy is greater.
b. In terms of costs per year-of-life saved, it is less expensive than when colonoscopy is the initial screening tool and the sensitivity for detecting small lesions is greater than conventional colonoscopy.
c. In terms of costs per year-of-life saved, it is more expensive than when colonoscopy is the initial screening tool and the sensitivity of colonoscopy is greater.
d. In terms of costs per year-of-life saved, it is more expensive than when colonoscopy is the initial screening tool but the increased sensitivity for detecting small lesions makes it the screening test of choice.
e. It eliminates all of the features of colonoscopy that cause patient discomfort and inconvenience.

10. Which of the following statements about the treatment of hepatitis C with interferon to prevent hepatocellular cancer is *true*?

a. Treatment has been shown to be beneficial at a stage when liver biopsy reveals no evidence for fibrosis and serum ALT levels are normal.
b. Treatment has been shown to be beneficial at a stage when liver biopsy reveals mild to moderate fibrosis and the serum ALT levels are less than twice normal.
c. Treatment has been shown to be beneficial at a stage when liver biopsy reveals cirrhosis and serum ALT levels are greater than twice normal.
d. Treatment is associated with reduced serum ALT levels and liver fibrosis but there has been no demonstrable effect on hepatocellular cancer development.
e. Treatment is too toxic for the majority of patients and leads to an unacceptable decline in quality of life.

11. Which statement is *true* regarding histologic transformation of follicular lymphoma?

a. It is a rare occurrence in patients with follicular lymphoma.
b. It happens commonly but does not affect the natural history of the disease.
c. It is readily treatable with CHOP.
d. It represents the emergence of a second malignant neoplasm unrelated to the first.
e. About half of patients may be cured with high-dose therapy and bone marrow transplant.

In Future Issues:

A Prognostic Index for Mylodysplasia