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INSIDE

After 16 Years: 'Watch and Wait' No Different than Immediate Therapy for Favorable Histology Lymphoma

ABSTRACT & COMMENTARY

Synopsis: *Currently, there is no curative treatment for advanced-stage, low-grade non-Hodgkin's lymphoma, and there remains a question of when to initiate treatment in the asymptomatic patient. In the current report from the British National Lymphoma Investigation, a long-term analysis of immediate (with single-agent oral chlorambucil) vs watchful waiting is reported. As has been previously reported from other series, there was no survival difference between those who received initial chemotherapy and those who were only started at a time of clinical progression. Almost 20% of those who were in the watchful-waiting arm had not required chemotherapy after 10 years on study, and for those 70 years and older, the actuarial chance of not needing chemotherapy was 40%.*

Source: Ardeshna KM, et al. *Lancet*. 2003;362:516-522.

FOR PATIENTS WITH ASYMPTOMATIC LOW-GRADE LYMPHOMAS (stage III or IV), there remains a question about the merits of immediate vs delayed treatment. Accordingly, in 1981 a multi-institutional UK study, the British National Lymphoma Investigation (BNLI) was initiated, and for approximately 10 years patients were randomly assigned to either immediate treatment (chlorambucil, 10 mg, administered orally daily) or watchful waiting. In the latter group, chlorambucil was administered when lymphoma progression necessitated treatment. Of the 309 randomized patients enrolled, 158 were to receive immediate treatment and 151 were to be observed without initial treatment. In both groups, local radiotherapy was permitted to symptomatic nodes.

As of the writing of this report, the median length of follow-up was 16 years. Overall survival or cause-specific survival did not differ between the 2 groups (median overall survival for the immediate treatment was 5.9 years (range, 0-17.8) and for the observation 6.7 years (0.5-18.9) ($P = 0.84$). The median cause-specific survival was 9 (0.5-17.8) and 9.1 (0.67-18.9) years, respectively ($P = 0.44$). In a multivariate analysis, age younger than 60 years, erythrocyte sedimentation rate (ESR) of less than 20 mm/hr, and stage III disease

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conferred significant advantages in both overall and cause-specific survival. In the observation group, at 10 years follow-up, 19 patients were alive and had not received chemotherapy. The actuarial chance of not needing chemotherapy at 10 years (with nonlymphoma deaths censured) was 19% (40% if older than 70 years).

■ COMMENT BY WILLIAM B. ERSHLER, MD

Although aggressive treatment regimens have been used, including combinations like CHOP or even more aggressive chemotherapy followed by stem cell rescue, there remains little evidence that advanced-stage, low-grade lymphoma can be cured by such treatments. Thus, in asymptomatic patients, the question of whether there is any advantage to immediate treatment was appropriately raised over 2 decades ago, and this and several other reports have addressed the question.[1-3] The BNLI project represents an advance because of its larger sample size and longer duration of follow-up. Nonetheless, the findings have all been consistent: There does not appear to be any benefit in immediate rather than delayed treatment in selected patients with low-grade lymphomas. The long-term follow-up provided by the current series is particularly valuable because of the indolent nature of the disease and the possibility that delays in therapy may, in some way, influence late recurrences and treatment responsiveness.

When the cohort that was randomized to watchful waiting was examined in the context of age at presentation, it is notable that for those older than 70, the chance of not needing chemotherapy was 40% after 10 years on study. Thus, for asymptomatic patients in this group, a strong case can be made for delaying treatment until clinical progression is evident inasmuch as this strategy quite possibly could prevent unnecessary treatment in a significant number of patients.

Of course, it is always possible that new and more effective treatments will prove better than single-agent chlorambucil, even though CHOP and similar regimens have failed to do so. Yet, a recent pilot study with CHOP plus rituximab has shown encouraging results, with more than 50% of patients not having progressed during a median follow-up period of 5 years.[4] In fact, rituximab alone was also recently shown to produce a response rate of 73% and a "molecular" remission in 57%.[5] The current role of rituximab in asymptomatic patients with low-grade lymphoma is a matter of active investigation, and exactly when to initiate treatment will become a critical question in this research. ■

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Port-Site Metastasis After Laparoscopic Surgery for Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *Port-site metastasis after laparoscopic surgery during chemotherapy, or when adequate chemotherapy has been given, is usually associated with poor outcome.*

Source: Huang K-G, et al. *Am J Obstet Gynecol*. 2003; 189:16-21.

In an attempt to define the clinical features and long-term prognosis of port-site metastasis after prima-

ry laparoscopic surgery for ovarian cancer, Huang and associates reviewed all patients with ovarian cancer who had undergone primary laparoscopic surgery at their institution. They then analyzed the clinicopathologic factors, presentation of port-site implants, management of the individual patient, long-term outcome, and several molecular biomarkers (flow cytometry, p53, p27, bax, HER-2/neu, and bcl-2). Of the 31 patients with epithelial ovarian cancer or borderline malignancy who underwent primary laparoscopic surgery over an 8-year period, 6 (19.4%) had port-site metastasis. Another 2 patients were referred after port-site metastasis. Those patients who had port-site metastasis develop during chemotherapy (n = 2) or after adequate chemotherapy treatment was given (n = 2) all died of cancer. Two patients were alive without disease; the tumors of these latter 2 patients were p27-positive and p53-negative, HER-2/neu-negative, and bcl-2-negative. Huang et al concluded that port-site metastasis after laparoscopic surgery during chemotherapy, or when adequate chemotherapy had been given, is usually associated with poor outcome. They also concluded that further investigations are necessary to define the mechanisms and effective management to prevent and treat this serious complication.

■ **COMMENT BY DAVID M. GERSHENSON, MD**

Minimally invasive surgery has clearly experienced a major resurgence in popularity among gynecologists over the past decade or so. This transformation has principally related to improvements in technology, including optics. Gynecologic oncology has not been immune from this change, and certain groups of oncologists have not only embraced these advances but have rapidly expanded indications for the use of operative laparoscopy. Minimally invasive surgery has been used extensively for surgical staging and restaging for various malignancies, primary surgical treatment of endometrial cancer, radical surgical techniques for cervical cancer, and for pelvic and paraaortic lymphadenectomy. While these procedures have been advocated by some groups for treatment of ovarian cancer, most gynecologic oncologists believe that there is no role for such in this malignancy. One of the major objections for its use in ovarian cancer has been the incidence of port-site metastases, although this complication has been reported in virtually all gynecologic cancers. However, laparoscopy has been used very effectively in the resection of benign adnexal masses; the problem lies in inability to accurately distinguish benign from malignant disease using currently available studies (ultrasound, serum CA 125, etc). The precise mechanism of port-site metastasis remains unclear, but pressure gradients and oxygen content have been implicated in its etiology. The present study simply relates this phenomenon to prognosis in patients treated with postoperative chemotherapy. Several strategies have been suggested to avoid this complication, including using gasless techniques, wound irrigation with saline or heparin, various topical agents, or immediate chemotherapy. The bottom line—laparoscopy should not be used in any patient with known ovarian cancer. ■

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

Postmastectomy Lymphedema: Laser Treatments May be the Answer for Some

ABSTRACT & COMMENTARY

Synopsis: *In a prospective, placebo-controlled trial, the use of 2 cycles of low-level laser therapy in women with postmastectomy lymphedema was shown to result in objective benefit in approximately one-third of cases. If further research confirms this finding, a new inexpensive and effective treatment modality will be available for this heretofore refractory consequence of breast cancer management.*

Source: Carati CJ, et al. *Cancer*. 2003;98:1114-1123.

Postmastectomy lymphedema remains a significant cause of morbidity for breast cancer patients, affecting up to 30% of patients who have received axillary node dissections and adjunctive radiotherapy.[1] Traditional treatments for this condition have included compression bandaging, manual lymphatic drainage, and extended limb elevation, but with only modest success.[2] In the current report from South Australia, Carati and colleagues explore the potential use of laser therapy in a randomized, placebo-control trial in patients with postmastectomy lymphedema. A total of 61 women were enrolled in the study—28 in the placebo group and 33 in the active treatment group. One treatment cycle consisted of 9 sessions (active laser or control) in which treatment was administered 3 times per week for 3 weeks. Briefly, for treatment, there was a grid with 17 points centered at 2-cm intervals placed in the axilla. The laser treatment head was held in contact with the skin adjacent to each point in the grid and

switched on for 1 minute at each point (total treatment time each session, 17 minutes). The total energy applied at each point was 300 mJoules for a total of 5.1 Joules over the 17 points on the grid, or 1.5 Joules/cm^2.

The outcome measures included an assessment of limb volume (perimetry), fluid distribution (bioimpedance), induration (tonometry), shoulder range of motion (goniometry), and a panel of subjective markers including self-reported symptoms, quality of life, and function.

There was no significant improvement immediately after treatments. However, by 1 month or 3 months of follow-up after 2 cycles of active laser treatment, 31% of subjects had a clinically significant reduction in arm volume (> 200 ccs). No effect was observed in the placebo treatment group or after only 1 cycle of laser treatment. The extracellular fluid index (by bioimpedance) of the affected and unaffected arms and torso were reported to be significantly reduced at 3 months after 2 cycles of laser therapy, and there was a significant softening of the tissues in the affected arm. Treatment did not appear to improve range of movement in the affected arm. With regard to the subjective measures, mean perceptual scores of symptoms and the index of activities of daily living demonstrated improvement after treatment in *all* groups (including placebo), and there was no difference found between active treatment and placebo in any of the measures except an improved quality of life score at 3 months after 2 cycles of treatment.

Thus, 2 cycles of laser treatment were found to be effective in reducing the volume of the affected arm, extracellular fluid, and tissue hardness in approximately one-third of patients with postmastectomy lymphedema at 3 months after treatment.

■ COMMENT BY WILLIAM B. ERSHLER, MD

The common appearance of lymphedema is frequently associated with physical discomfort (pain, heaviness), impaired function, and reduced quality of life. Standard approaches have offered only modest improvements, and the introduction of a new treatment modality with promise for success in one-third of patients would be a significant clinical advance. The current trial included a relatively small number of patients, but the design of the study was solid (prospective, randomized, placebo controlled), and the results clearly demonstrate benefit for some patients. As Carati et al acknowledge, a great deal more research will be needed to determine the optimal treatment dose and schedule, the duration of effect, and whether there is any long-term negative consequence.

Certainly, additional research should also be directed at determining the mechanisms involved in producing reduced lymphedema. Laser treatment for other conditions has been shown to affect fibroblast proliferation,[3] macrophage and lymphocyte functions,[4,5] and, perhaps most importantly in this context, to stimulate lymphangiogenesis.[6] It is conceivable that these or other mechanisms yet to be described are involved in the treatment responses. Furthermore, it is also conceivable that laser treatment may activate dormant metastatic cells, and very careful analysis in larger trials will be required to determine the overall safety of this approach.

With regard to feasibility, it should be pointed out that the equipment required is relatively inexpensive (estimated to be approximately US $5000) and the treatments administered are of short enough duration that an economic analysis would likely show the overall costs to be low.

Thus, an intriguing new approach to a long-standing problem in cancer management has recently been introduced. The use of low-level laser therapy for the treatment of postmastectomy lymphedema deserves vigorous exploration. ■

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CNS Lymphoma and Thrombosis

ABSTRACT & COMMENTARY

Synopsis: *Although a high incidence of thrombotic events is reported for primary brain tumors, the incidence in patients with CNS lymphoma is previously unreported. In a retrospective review from a single institution, 25 of 42 patients with CNS lymphoma experienced venous thromboembolism, and in 3 cases the event was fatal. Although the data now available are retrospective and from a single institution, a case for prophylactic anticoagulation is made, particularly during the treatment phase of this disorder.*

Source: Goldschmidt N, et al. *Cancer*. 2003;98: 1239-1242.

VENOUS THROMBOSIS OCCURS COMMONLY IN patients with malignancy, perhaps as often as in 15% of patients. Patients with glioblastomas and other

primary brain tumors are at particularly increased risk. Goldschmidt and colleagues at the Hadassah-Hebrew University Hospital in Jerusalem performed a retrospective analysis of 42 patients with CNS lymphoma treated at their center to determine the risk of venous thrombosis in patients with this tumor type. Of the 42 CNS lymphoma patients seen between 1992 and 2001, 25 patients (59.5%) had venous thrombosis, and 3 patients (7%) died of overwhelming pulmonary embolus. Fourteen of the 25 patients had DVT of lower extremities, and 11 patients had pulmonary emboli, 5 of whom had no demonstrable DVT.

The majority of the DVT events occurred during the early period of treatment. Goldschmidt and colleagues suggest that anticoagulation be provided to prevent DVT in patients with CNS lymphoma.

■ **COMMENT BY WILLIAM B. ERSHLER, MD**

The incidence of thromboembolism is notable in patients with cancer in general, but is particularly prominent in patients with both primary brain tumors and lymphomas. In patients with brain tumors, the occurrence in some series is as high as 28%.[1] Risk factors include leg paresis, a histological diagnosis of glioblastoma multiforme, age 60 years or older, large tumor size, the use of chemotherapy, and length of surgery of > 4 hours.[2] In patients with lymphoma, the incidence of thromboembolism ranges between 6.6% and 13.3%,[3,4] and in many cases it has been attributed to venous obstruction by bulky lymphadenopathy or to indwelling venous catheters. In the current series of CNS lymphoma patients, the incidence was considerably higher—nearly 60%. Goldschmidt et al speculate that the reason for the higher incidence relates to the risks associated with CNS disease, as well as certain hypercoagulable factors observed in patients with lymphoma. Furthermore, patients in their series were subjected to intensive chemotherapy regimens, and it was noted that thromboembolism in the great majority of cases occurred within several weeks of the start of chemotherapy. Chemotherapy has been shown to induce a hypercoagulable state by reducing levels of protein C and S[5] and antithrombin III.[6] Furthermore, methotrexate and carboplatin (one or the other was used in the majority in this series) can enhance the thrombogenic tendency by elevating levels of homocysteine or von Willebrand factor, respectively.[4,7]

Thus, this series, albeit from a single institution and subject to all the concerns of a retrospective analysis, is likely to accurately reflect a high incidence of thrombotic events in patients with CNS lymphoma. It is tempting to conclude that all such patients should be anticoagulated, at least during the time they are receiving intensive chemotherapy. To strengthen this argument, the same group of investigators has embarked upon a prospective study using low-molecular-weight heparin in all patients with CNS lymphoma. Their very preliminary results, mentioned in the Discussion section of the current report, indicate that there have been no thrombotic events and no hemorrhagic complications among the first 10 patients at a median duration of 14 months. Hopefully, the report of this study will be available soon. In the meantime, clinicians should consider the impressive findings from this 1 retrospective review and consider anticoagulation in patients with CNS lymphoma. ■

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Phase II Study of Capecitabine and Oxaliplatin as First-Line Treatment in Advanced Colorectal Cancer

ABSTRACT & COMMENTARY

Synopsis: *Combining capecitabine and oxaliplatin yields promising activity in advanced colorectal cancer; therefore, the capecitabine dose we used is probably too high. The main toxicity is diarrhea, which is manageable with appropriate dose reductions. This combination may be preferable compared to a standard combination with infusional fluorouracil/leucovorin, as it is more convenient and practical with similar efficacy. Thus, phase III trials are needed to clarify its role in the treatment of chemotherapy-naive advanced colorectal cancer patients.*

Source: Zeuli M, et al. *Ann Oncol*. 2003;14:1378-1382.

THERE IS A NEED FOR MORE EFFECTIVE AND LESS toxic therapy for patients with metastatic col-

orectal cancer. 5-fluorouracil is still one of the most important drugs in the treatment of both adjuvant and metastatic disease. Continuous infusion has been shown to be superior to intravenous bolus injection. The limitation of the infusion has been the cost, inconvenience, discomfort, and potential risks of the need for an indwelling central venous catheter. Oxaliplatin has entered clinical practice with the demonstration of its efficacy with a number of infusional regimens.[1] It has already been demonstrated that capecitabine is superior to bolus 5-fluorouracil/leucovorin in the treatment of metastatic colorectal cancer.[2] It has been incorporated in the regimens with oxaliplatin as a substitute for the infusional 5-fluorouracil component.[3] The present study expands this experience and the search for the optimal dose of this combination.

■ **COMMENT BY STUART M. LICHTMAN, MD, FACP**

Patients with histologically proven advanced adenocarcinoma of the colon or rectum were eligible for this study. They had to be not pretreated with chemotherapy for advanced disease and had to have completed adjuvant chemotherapy 6 months before study entry. All patients were required to have World Health Organization performance status (PS) < 2, aged between 18 and 75 years, life expectancy > 12 weeks. The regimen consisted of capecitabine 2500 mg/m^2/d in combination with oxaliplatin 120 mg/m^2. Twenty-nine patients had primary colon, and 14 had rectal cancer. A total of 211 cycles of chemotherapy was delivered with a median of 5 cycles per patient (range, 1-11). Twenty-five patients (58%) had a PS of 0, and 18 patients (42%) had a PS of 1. Eighteen patients received adjuvant chemotherapy, 11 with a bolus 5-fluorouracil/leucovorin regimen and 3 with the de Gramont regimen and 4 received concomitant chemo-radiotherapy with infusional 5-FU. The majority of patients had liver (53%) or lung (37%) metastases. Twenty-five patients (58%) had only 1 site of disease, 13 (30%) had 2 sites and 5 (12%) had 3 or more. The toxicity of the regimen peaked in the first three cycles and was then reduced in the following cycles because of dose modifications. The main toxicity was grade 3 or 4 diarrhea, which occurred in 28% of the patients. Its incidence was cycle dependent, 13 out of 19 cases of severe diarrhea being observed during the first 3 cycles. Grade 3 or 4 nausea and vomiting occurred in 5% and severe sensory neuropathy in 7% of patients. Neurotoxicity was observed most frequently after 3 cycles of treatment. Laryngospasm during the oxaliplatin infusion was observed in 2 patients and was prevented in the following treatment cycles by prolonging the oxaliplatin infusion duration. Stomatitis was mild and rarely observed with this treatment combination. Hematological toxicity was moderate. Grade 3 neutropenia occurred in 2 patients, but 1 case of life-threatening febrile neutropenia was reported. One patient had uncomplicated thrombocytopenia grade 4. Mild anemia occurred in 12 patients. The response rates were 44% and 48.7% (95% CI, 33.0-64.4%) (intention-to-treat and per protocol analysis, respectively). The median overall survival was 20 months.

The results of this phase II study establish the feasibility and efficacy of combining capecitabine with oxaliplatin in advanced colorectal cancer. The 48% response rate in nonpretreated patients compares well with the 50.7-53% objective responses observed with oxaliplatin plus continuous infusion fluorouracil/leucovorin in first-line treatment. Besides efficacy, toxicity is a critical end point with which to assess the benefit of a new treatment combination. In this study, Zeuli and colleagues attempted to use the drugs in combinations in the same doses that are recommended for single-agent therapy. This may have been too high, particularly for the capecitabine. In conclusion, combining oxaliplatin with capecitabine may be preferable compared with a standard combination with infusional fluorouracil/leucovorin, as it is more convenient and practical with similar efficacy and toxicity. A recent trial has been reported with dosing recommendations of capecitabine in combination with oxaliplatin 130 mg/m^2 at an initial dose of 1250 mg/m^2 2 times daily in untreated patients and at a dose of 1000 mg/m^2 2 times daily in pretreated patients.[4] In elderly patients, similar efficacy was seen with lower doses of oxaliplatin (85-100 mg/m^2) and capecitabine 1000 mg/m^2 2 times daily.[5] Phase III trials are needed to clarify the role of the combination of capecitabine and oxaliplatin in the treatment of patients with advanced colorectal cancer. The dose of both oxaliplatin and capecitabine need to be further clarified. Studies are particularly important in previously treated patients, the elderly and those with a poor performance status. ■

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Intraperitoneal Radioactive Phosphorus (32P) vs Observation After Negative Second-Look Laparotomy for Stage III Ovarian Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Intraperitoneal chromic phosphate did not decrease the risk of relapse or improve survival for patients with stage III epithelial ovarian cancer after a negative second-look surgery.*

Source: Varia MA, et al. *J Clin Oncol.* 2003;21: 2849-2855.

In a gynecologic oncology group study, varia and colleagues reported that 202 patients with negative second-look surgery were randomized to either intraperitoneal chromic phosphate or no further therapy. With a median follow-up of 63 months in living patients, 68 patients in the treatment group (65%) and 63 patients in the observation group (64%) developed tumor recurrence. The relative risk of recurrence was 0.90 (90% confidence interval [CI], 0.68-1.19). The 5-year relapse-free survival rate was 42% and 36% for the treatment and observation groups, respectively; the difference was not statistically significant. There was no statistically significant difference in overall survival. The relative risk of death was 0.85. Sixteen patients (8%) experienced grade 3 or 4 adverse effects, with 8 in each group. Varia et al concluded that intraperitoneal chromic phosphate did not decrease the risk of relapse or improve survival for patients with stage III epithelial ovarian cancer after negative second-look surgery. Despite complete pathologic remission at second-look after initial surgery and platinum-based chemotherapy, 61% of stage III ovarian cancer patients had tumor recurrence within 5 years of negative second-look surgery. They further concluded that these findings indicate a need for more effective initial therapy and further studies of consolidation therapy.

■ **COMMENT BY DAVID M. GERSHENSON, MD**

One of the greatest challenges facing oncologists is to improve the cure rate of patients with advanced epithelial ovarian cancer. Currently, only about 20% of patients with stage III disease and less than 5% of those with stage IV are cured. Although a very high percentage of patients (60-70%) are clinically disease-free following standard therapy consisting of primary cytoreductive surgery followed by combination chemotherapy with paclitaxel and carboplatin, most of these patients eventually relapse and die of their cancers. Even with negative findings on second-look surgery performed to assess disease status, up to 50% of patients will have false-negative findings and succumb to their disease. In other words, we are able to achieve minimal, microscopic, or surgically undetectable tumor burden in most patients but unable to completely eradicate the malignancy with our current approach. Several strategies have been considered or tested in this most favorable group of patients—those with negative second-look surgery findings—in an attempt to reduce the disappointing relapse rate. Whole abdominal radiotherapy has been investigated, and essentially all studies reveal no improvement in disease-free survival plus a disturbingly high rate of intestinal injury secondary to radiation. Consolidation chemotherapy has thus far been found to prolong progression-free survival but has not been demonstrated to improve overall survival. This randomized trial tests intraperitoneal chromic phosphate—a treatment used for decades in various settings for ovarian cancer—but without evidence of a favorable effect on either relapse-free survival or overall survival. Therefore, the search continues for effective consolidation therapy to achieve a superior outcome. Although second-look surgery has essentially disappeared from the scene, the surrogate group for future trials will be patients who are clinically disease-free at the conclusion of primary treatment. ■

CME Questions

14. Regarding the occurence of venous thromboembolic events in patients with CNS lymphoma, which of the following statements is true?

a. It is likely to be no more frequent than in the general cancer population.
b. It is likely to be more frequent than in the general cancer population, but less frequent than that observed for gliomas or systemic lymphoma.
c. It is likely to be more frequent than in the general cancer population, and also more frequent than that observed in patients with systemic lymphoma or glioma.
d. It has been demonstrated to be preventable by prophylactic low molecular weight heparin.

15. Which of the following treatment choices has proven superior with regard to overall survival for asymptomatic patients with stage IV low-grade lymphoma?

a. Daily oral chlorambucil
b. Six cycles of CHOP, administered every 3 weeks (French CHOP)
c. Allogeneic bone marrow transplantation
d. Watchful waiting
e. None of the above

16. Low-level laser therapy has been shown to:

a. reduce fluid volume in the affected arm of approximately 33% of women with postmenopausal lymphedema.
b. reduce fluid volume in the affected arm of approximately 66% of women with postmenopausal lymphedema.
c. have no effect on fluid volume in the affected arm of women with postmenopausal lymphedema but significantly enhance quality of life in one-third of treated patients.
d. have no effect on fluid volume or quality of life in the affected arm of women with postmenopausal lymphedema but significantly enhance range of motion in the shoulder of treated patients.

Answers: 14(c); 15 (e); 16 (a)

In Future Issues:

G-CSF for Primary Prophylaxis in CHOP-Treated Elderly Lymphoma Patients