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INSIDE

Ovarian Autotransplantation Prior to Pelvic Radiation: A Novel Strategy to Preserve Hormonal Function in Premenopausal Patients

ABSTRACT & COMMENTARY

Synopsis: *In a single case report of young woman with cervical cancer, an autologous transplant of one ovary to an area outside of proposed radiation therapy was demonstrated to be effective at maintaining ovarian function. The procedure was done at the time of radical hysterectomy by a second surgical team. Thus, a novel approach may ultimately be available for preserving hormonal and reproductive ovarian function and quality of life for premenopausal patients requiring pelvic radiation.*

Source: Hilders CG, et al. *Cancer*. 2004;101:2771-2778.

With the addition of radiation and chemotherapy to the standard surgical treatment, young women with cervical cancer are now experiencing higher complete remission and cure rates.[1] These benefits, however, are often clouded by the morbidity associated with early menopause and loss of fertility.[2] Depending on dose, duration and extent of treatment, radiation results in direct cellular damage—causing atrophy and reduced follicle stores.[3] Attempts at gonadal functional maintenance, such as by cryopreservation or transplantation have been examined extensively, but follicular loss secondary to ischemia has remained a rate-limiting factor in their success.[4] Thus, Hilders and colleagues studied the role of heterotopic autotransplantation using microscopic anastomosis to protect and maintain ovarian function and vitality.

The results from a single patient were extensively detailed in this report. The patient was found to have a large squamous cell carcinoma (FIGO Stage Ib2) and was treated by ovarian transplantation, followed by radical hysterectomy with pelvic node dissection. The patient's left ovary was transplanted to her left upper arm, and vascular anastomosis was successfully achieved by microsurgical techniques. Using different diagnostic modalities, the transplanted ovary

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was demonstrated to have preserved ovarian function, including adequate blood flow, regularity in cycle and normal follicular growth for greater than one year. Thus, autotransplantation was successful and found to spare the ovary from potential radiation induced cellular damage.

COMMENT BY WILLIAM B. ERSHLER, MD

This detailed report is the second case in which an ovary was excised and transplanted outside of a radiation field in an effort to preserve reproductive and hormonal function. The procedure was performed coincident with radical hysterectomy and there was no added anesthesia or postoperative complication. It is encouraging that at one year, the organ continues to function although additional follow-up is clearly needed to establish an expected duration benefit. Nonetheless, this procedure, once developed and demonstrated to be safe and effective, may well enhance the quality of life for female patients with pelvic disease requiring radiation therapy for cure.

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EDITORIAL GROUP HEAD: Lee Landenberger.
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Phase II Randomized Trial of Vinorelbine and Gemcitabine vs Carboplatin and Paclitaxel in Advanced Non-Small-Cell Lung Cancer

ABSTRACT & COMMENTARY

Synopsis: *This study was designed to compare overall toxicity and quality of life between the 2 regimens: vinorelbine and gemcitabine (VG) vs carboplatin and paclitaxel (CP).*

Source: Lilenbaum RC, et al. *Ann Oncol*. 2005;16:97-101.

THE PURPOSE OF THIS STUDY WAS TO COMPARE QUALity of life and overall toxicity in patients with advanced non-small-cell lung cancer (NSCLC) treated with VG or CP. Patients with advanced non-small-cell lung cancer are frequently treated with a platinum-based regimen. Platinum-based doublets have comparable efficacy but slightly different toxicity profiles. Compared to single-agent therapy, platinum-based combinations tend to improve survival without a detriment in quality of life. Non-platinum combinations were developed in an attempt to decrease toxic effects associated with the platinum compounds. Non-platinum regimens based on the taxanes, paclitaxel, and docetaxel, usually in combination with gemcitabine, have been compared to standard platinum doublets in randomized trials. Overall survival was not statistically different, but toxicity did not seem to be improved with the taxane-based regimens. Among the non-platinum, non-taxane combinations, VG is the most extensively tested. In phase II trials in advanced NSCLC, VG showed efficacy comparable to platinum combinations and a seemingly more favorable toxicity profile. In recent phase III studies, the combination of VG was compared with cisplatin-based doublets. Overall, there was no significant difference in survival, but toxicity was indeed less pronounced.

COMMENT BY STUART M. LICHTMAN, MD

The eligibility of the trial included patients with a confirmed diagnosis of stage IIIB or IV NSCLC were eligible if they were 18 years old or older, had an ECOG

performance status of 0 to 2, and received no prior chemotherapy. Patients were randomized to receive vinorelbine 25 mg/m^2 i.v. plus gemcitabine 1000 mg/m^2 i.v., both given on days 1 and 8, every 21 days, or paclitaxel 200 mg/m^2 i.v. plus carboplatin dosed to an area under the curve (AUC) of 6 according to the Calvert formula, both administered on day 1 every 21 days. The primary end point of the trial was quality of life (QoL) assessed by the Lung Cancer Symptom Scale (LCSS).[1] The LCSS instrument is composed of 2 components: a 9-item patient self-administered questionnaire and a 6-item component completed by health care professionals. Within the 9-item patient questionnaire, 6 major symptoms are captured (loss of appetite, fatigue, cough, dyspnea, hemoptysis, and pain), as well as overall symptomatic distress, functional activity and global QoL; all components were evaluated using a visual analogue scale in which scores for lowest to highest symptom intensity or functional disability corresponded to lengths on the VAS ranging from 0 to 100 mm, respectively. The 6 items in the observer instrument were also scored from 0 to 100, however in increments of 25 points and with scores reversed from the patient-scored instrument (100 = none and 0 = severe). For both the patient and observer scores, a mean was taken across all component scores to provide an overall index. The LCSS was administered at week 1 of cycle 1 and at 3-week intervals regardless of modifications of the treatment schedule.

A total of 165 patients (82 for VG and 83 for CP) were enrolled from 25 participating centers. The median age was 64.4 years (range, 38-86 years). Approximately 82% of the patients had stage IV and 85% had a performance status of 0-1. The 2 arms were well balanced with regard to demographics and baseline parameters. The median number of cycles was 4 in both arms, with 40% and 41% completing all 6 cycles in arms VG and CP, respectively. The primary reason for discontinuation of treatment was disease progression in both arms. Hematologic toxicity, specifically grade 3-4 neutropenia, was more common in CP (21.7%) compared to VG (8.5%) ($P = 0.019$). Thrombocytopenia (grades 3-4) was also more common in CP than VG (9.6% vs 1.2%) ($P = 0.017$). Two patients in the VG arm had febrile neutropenia. No treatment-related deaths occurred. For the patient-rated evaluations of the LCSS, baseline scores were around 32 mm for both groups (with 0 and 100 mm indicating best and worst QoL, respectively). Slight increases were seen for the mean change from baseline for the VG group for the first 3 cycles, whereas slight decreases were seen in the mean changes from base line for the CP group for the first 4 cycles; none of the differences between groups achieved the 10 mm difference planned. Using the mixed effects longitudinal modeling, no statistical differences were found between the treatment groups. Efficacy parameters were comparable between the 2 treatments. The overall response rate was 14.6% in VG and 16.9% in CP. In addition, 37.8% and 36.1% of patients in VG and CP, respectively, achieved stabilization of their disease. Median time to progression was 3.9 months for VG and 4.8 months for CP. Median survival was 7.8 months for VG and 8.6 months for CP. One-year survival rates were 38.4% for the VG arm and 31.9% for the CP arm. None of the efficacy parameters were significantly different between the 2 treatment arms.

The development of non-platinum regimens was based on the premise of equivalent efficacy with lower overall toxicity. The non-platinum, taxane-based regimens showed comparable survival as standard platinum-based doublets. In the study by Smit and colleagues, progression-free survival was slightly inferior with paclitaxel-gemcitabine compared to the platinum regimens, but no significant difference in overall survival was noted.[2] However, more importantly, overall toxicity was not reduced significantly with the non-platinum regimen. While paclitaxel or docetaxel, in combination with gemcitabine, can be considered a reasonable option for first-line therapy for advanced NSCLC patients, the available data do not support a significant advantage in toxicity over platinum-based regimens. The VG combination seemed to produce lower hematologic toxicity, lower neuropathy, and lower alopecia, when indirectly compared to more standard combinations. Therefore, it was chosen to compare this regimen to CP, the most widely used platinum-based doublet. Treatment was well tolerated in both arms. However, there were notable differences in hematologic and non-hematologic toxicity. VG resulted in a lower incidence of severe neutropenia and all grades of thrombocytopenia. In addition, peripheral neuropathy and alopecia were reduced in patients treated with VG. Although some of these toxic effects are likely to impact on the quality of life of individual patients, the LCSS QoL analysis showed no significant difference between the 2 treatments. These results were similar to those reported by Gridelli and colleagues.[3] In the accompanying editorial, Dr. Joan Schiller concluded that VG represents a viable option for patients concerned about certain treatment-related toxic effects.[4] Indeed, the 2003 American Society of Clinical Oncology guidelines for the treatment of NSCLC consider non-platinum regimens an appropriate alternative to platinum-based chemotherapy.[5] This regimen may also be appropriate for the elderly and possibly poor performance status patient.[4,7-9]

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Hyper-CVAD as Initial Treatment for ALL

ABSTRACT & COMMENTARY

Synopsis: *The chemotherapy regimen Hyper-CVAD is increasingly used for patients with hematological malignancies. In this report from the MD Anderson Cancer Center, clinical outcomes for 288 adults who received first-line treatment with this regimen for acute lymphocytic leukemia were presented. Overall complete response rate was 92%, induction mortality was 5% and the 5-year CR duration was 38%. These results warrant additional consideration of this regimen for initial therapy by comparing it with more commonly used regimens in a large, cooperative group trial.*

Source: Kantarjian H, et al. *Cancer*. 2004;101:2788-2801.

Intensive chemotherapy regimens have increased the response rate and long-term outcome for patients with adult acute lymphocytic leukemia (ALL). Prior to modern therapeutic approaches, a slow response to induction chemotherapy, older age, and the demonstration of either Philadelphia chromosome or T-cell markers were shown to be negative prognostic indicators.[1,2] With newer regimens including Hyper-CVAD, greater than 80% of patients achieve complete responses and long-term survival rates have occurred in 30% to 40%.[3] In the current report, Kantarjian and colleagues from MD Anderson report the complete remissions (CR) and long-term survival rates for a large series of adults with ALL treated with the Hyper-CVAD chemotherapy regimen.

The researchers reviewed the outcomes of 288 patients who were treated with Hyper-CVAD between 1992 and 2000 at MD Anderson. This complex regimen includes alternating cycles of cyclophosphamide, daunorubicin vincristine and dexamethasone with high-dose cytosine arabinoside and methotrexate.[2] In this series, the median age was 40 years and 20% were older than age 60. The incidence of T-Cell ALL was 13% and Philadelphia chromosome was demonstrable in 17%. Complete remission was achieved in more than 90% and at 63 months there was a 30-45% overall survival rate. Prognostic factors that influenced outcome were identified as age, performance score, hepatomegaly, leukocyte and platelet counts, albumin and bilirubin levels, FAB classification, immunophenotype, karyotype and myeloid markers. After dividing participants into low risk, intermediate risk, and poor risk groups based on a multivariate analysis of these prognostic factors, 5-year CR duration rates were found to be 52%, 37%, and 10%, respectively. Overall results of the Hyper-CVAD regimen were found to be favorable and were significantly better when compared to the previous CVAD regimens.

COMMENT BY WILLIAM B. ERSHLER, MD

The Hyper-CVAD regimen, developed initially for the treatment of ALL, has been used with benefit for a variety of other hematological malignancies including lymphoblastic lymphoma, mantle cell lymphoma, multiple myeloma, and Richter's transformation of chronic lymphocytic leukemia.[4-7] Although the current report is that of a non-randomized population of adults with ALL treated at a single institution, the findings are remarkable because of the high response and long-term survival rate. Comparison with other published reports of front-line ALL treatment[8,9] is problematic inasmuch as there was a higher percentage of older patients and patients with other negative prognostic factors in the current series. Thus, Hyper-CVAD is a very reasonable first-line approach to the management of ALL. The findings of a 92% CR rate, an induction mortality rate of 5%, a median survival of 32 months, and a 5-year survival rate of 38% is as good as has ever reported, particularly because of the inclusion of higher-risk patients. Future cooperative group trials will hopefully include this regimen to determine if these improved numbers are reproducible outside of the large cancer center from which they were generated. Furthermore, the regimen might be altered to some degree under certain circumstances, such as the inclusion of imatinib for those with Ph-positive ALL, or incorporating monoclonal antibody therapy in patient whose leukemic cells express the appropriate target (eg, rituximab if CD20 positive, alemtuzumab if CD52 positive or gemtuzumab if CD33 positive). These alterations, too, should be subjected to clinical trial before assuming the designation as standard of care. ■

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Initial Treatment for Non-Bulky Hodgkin's Disease: Lack of Benefit from Combined Modality

ABSTRACT & COMMENTARY

Synopsis: *Effective initial treatment for early stage Hodgkin's disease can include radiation or chemotherapy, or both. In a randomized study conducted at Memorial Sloan Kettering, patients with stage I, II, or IIIA disease (non-bulky) were randomized to receive radiation plus chemotherapy or chemotherapy alone. There were no differences observed in remission rate or duration or overall survival.*

Source: Straus DJ, et al. *Blood*. 2004;104(12):3484-3489.

Several therapeutic regimens have been used in the treatment of early stage Hodgkin's disease. Between 1975 and 1986, different combinations of chemotherapy were added to the standard treatment of radiation therapy, demonstrating improved clinical outcomes.[1,2] Various chemotherapy regimens were investigated with the goal of maintaining the high level of response while reducing toxicity. The question remains, however, whether chemotherapy alone would achieve the high level of clinical response as combined modality therapy (CMT). Straus and associates conducted a single institution (Memorial Sloan Kettering) randomized, prospective study aimed to determine whether differences in outcome are achieved with CMT vs chemotherapy (CT) alone in the treatment of nonbulky Hodgkin's disease.[3] The researchers hypothesized that CMT would be superior to CT in freedom from progression (FFP) and overall survival (OS).

One hundred fifty-two patients with Hodgkin's disease stages IA, IB, IIA, IIB, or IIIA were randomized to 6 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) alone or ABVD followed by radiation therapy (RT). Of the 65 patients who received RT after ABVD, 94% achieved complete remission (CR) while 6% demonstrated no significant response. The ABVD group achieved 94% CR while 1.5% showed partial response (PR) and 4.5% had no significant response. No overall significant difference was noted between the two groups in CR, PR, FFP and OS (after 60 months CR duration).

COMMENT BY WILLIAM B. ERSHLER, MD

This report describes the results from a single institution of a randomized trial of ABVD + radiation therapy vs ABVD alone for the treatment of stage I, II or IIIA non-bulky Hodgkin's disease. It was conducted over a 10-year period and no significant differences were observed in the relevant clinical parameters of remission rate, duration of remission and overall survival. However, Straus et al noted that at 60 months, overall survival in the combined modality arm was 97% compared to 90% in the chemotherapy alone arm (P = .08) and they speculated that this difference might prove significant in a larger trial.

What is missing in this report, but covered succinctly in the accompanying editorial[4] is the weight of evidence of long-term consequences of radiation, particularly the occurrence of second malignancies.[5-7] Ng and colleagues[5] have estimated the death rate from second malignancies in radiation treated Hodgkin's patients to be approximately 10% based on a median follow-up of 12 years in patients who were treated before the age of 50 years. Accordingly, it is quite possible that more radiation-treated Hodgkin's patients will die of complications of therapy than of Hodgkin's disease, itself.

Thus, the optimal treatment for early stage Hodgkin's disease, despite decades of available effective approaches, remains controversial. What the Memorial experience has shown is that combined modality does not offer significant advantage for initial treatment of non-bulky disease. Thus, it would seem prudent that such patients be treated initially with combination chemotherapy, and radiation be reserved for those who fail to enter complete remission or who relapse with disease. ■

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Weekly Taxotere for Lung Cancer

ABSTRACT & COMMENTARY

Synopsis: *Weekly docetaxel was compared with the traditional every 3-week schedule in patients with advanced lung cancer after failure with a platinum-based regimen. There was no significant difference in efficacy in terms of time to progression or overall survival, but neutropenia was significantly more common for those receiving the drug at 3-week intervals. In contrast, asthenia was more common in the weekly treated patients. This may be due to the more sustained exposure to corticosteroid premedication.*

Source: Gervais R, et al. *Ann Oncol*. 2005;16:90-96.

Docetaxel administered at a dose of 75 mg/m^2 every 3 weeks is considered a standard second line approach for patients with non-small-cell carcinoma (NSCLC) of the lung when discovered to have progressive disease after initial platinum-based chemotherapy. Weekly docetaxel at a lower dose is also used in this setting and may be less toxic. Gervais and colleagues from Strasbourg randomized 125 patients with locally advanced or metastatic NSCLC after failure of a previous platinum-based regimen to receive either docetaxel 75 mg/m^2 administered every 3 weeks or docetaxel 40 mg/m^2 given weekly for 6 weeks followed by 2 weeks of rest.

Median time to progression and survival were similar between the 2 groups (2.1 and 5.8 months for the q3W arm compared to 1.8 and 5.5 months for the qW group). However, grade 3-4 neutropenia occured in 48.4% of the q3W treated patients vs 15.9% of the qW patients (P = 0.001). In addition, febrile neutropenia was observed in 6.5% of patiens in the q3W arm vs 0% in the qW arm. In contrast, asthenia was more frequent in the qW group.

Thus, weekly docetaxel is an alternative second-line approach for the treatment of NSCLC, comparable in efficacy to q3W dosing but with less resultant neutropenia.

COMMENT BY WILLIAM B. ERSHLER, MD

Docetaxel has become widely used for a variety of malignant conditions including lung, breast, and prostate cancer. For lung cancer, it is most frequently used as a second-line agent and in a q 3 week schedule. However, it has been widely appreciated, if not scientifically demonstrated, that weekly treatment is comparable in efficacy and less toxic. Thus, the findings of Gervais et al come as no surprise, albeit the difference with regard to neutropenia was a bit more than expected.

The profile of tumors for which docetaxel is active includes those common in elderly patients (lung, prostate, and breast). Older people are known to have compromised marrow reserve and more frequent episodes of neutropenia. Thus, weekly therapy may well be most effective in this setting. In this regard, the increased asthenia observed with weekly therapy is of concern, because this, also, is likely to be more of a problem for elderly patients. The asthenia may be the result of the common practice of premedicating with corticosteroids. On this trial, those randomized to weekly therapy were to receive 8 mg of dexamethsone (or comparable prednisone or methylprednisilone) on 3 occasions with each weekly dose of docetaxel. Although this was less than the 6 doses given to those on the q3W schedule, over the course of 6 weeks, this amounts fairly high dose, sustained corticosteroid treatment. It is quite possible that the higher incidence of asthenia is thereby explained. Currently, the Geriatric Oncology Consortium is investigating the level of steroid needed to prevent adverse consequences (fluid retention) in lung cancer patients receiving weekly docetaxel therapy.

Immunotherapy for Consolidation Treatment of Ovarian Cancer—Is This the One?

ABSTRACT & COMMENTARY

Synopsis: *Consolidation therapy with oregovomab did not significantly improve TTR overall. A set of confirmatory phase III studies has been initiated to determine whether the successful front-line therapy population derives benefit from oregovomab treatment.*

Source: Berek JS, et al. *J Clin Oncol*. 2004;22:3507-3516.

It has been well described and consistently reported that more than half of advanced ovarian cancer patients achieving complete clinical remission (CCR) following primary surgery and chemotherapy will ultimately recur—the majority within 3 years of treatment completion. This observation has prompted many clinicians and researchers to evaluate alternative treatment strategies to improve, in the short term, the

duration of remission—in the long term, overall survival. Berek and colleagues evaluated a novel immunotherapeutic agent, oregovomab (Ovarex™), in this setting with the primary objective of improving time-to-treatment relapse (TTR).

The study methodology was a randomized, double-blinded, placebo controlled trial in which patients who had undergone a maximal effort at surgery and chemotherapy and who had achieved CCR were offered participation. The agent, oregovomab, is a murine-derived monoclonal antibody with high affinity for CA-125—the tumor-associated antigen present in more than 90% of non-mucinous epithelial ovarian cancers. Oregovomab, or placebo, was administered to patients at baseline, 4 weeks and 8 weeks after enrollment and then every 12 weeks to 2 years in the absence of tumor progression or toxicity. Tumor recurrence was documented by CT imagery, as the effect of CA-125 immunotherapy on endogenous CA-125 values was not known. Although collected, these values were blinded to Berek as well. Enrollment goals were powered to detect a 50% improvement in TTR with oregovomab. Stratification variables as well as quality-of-life (QOL) parameters were assessed. Overall, the therapy was well tolerated, with few severe adverse events recorded. Likewise, QOL parameters were seemingly unaffected by treatment compared to placebo. Unfortunately, the primary end points were not achieved—no improvement in TTR was detected with oregovomab therapy (13.3 mos vs 10.3 mos; $P = 0.71$).

Survival data were immature and not presented. In the evaluation of risks for relapse, performance status, CA-125 values before the third cycle of chemotherapy, and baseline CA-125 values were identified as prognostic. Subgroup analysis taking these factors into account identified a population that may benefit from oregovomab therapy, demonstrating more than twice the median TTR in treated patients vs controls. Berek et al concluded that while this consolidation strategy did not significantly improve TTR, the exploratory, hypothesis-generating subgroup analysis provided information to support planned and ongoing clinical trials in selected patients.

COMMENT BY ROBERT L. COLEMAN, MD

One of the more difficult aspects of ovarian cancer management is making a solid and convincing recommendation regarding "what to do next" following initial successful therapy. At our disposal are a smorgasbord of options including surgery, observation and additional therapy. Currently, while surgery predominately represents another diagnostic modality for treatment planning, the "second-look" or "reassessment" operation itself is generally not considered standard therapy because we have yet to clearly document that doing the procedure actually improves survival. Indeed, even among those patients deemed in complete remission by pathological assessment, approximately 40-50% will ultimately recur. This event occurs principally from growth of undocumented foci of microscopic or small-volume residual disease. In this regard, additional or consolidation therapy is aimed at addressing this (likely present) disease. Informed counseling involves explaining these clinical facts, providing some estimation of their personal recurrence risk (based on previous findings at surgery, response to therapy by direct or surrogate measures and current disease status) and reviewing the clinical data of trials that have been conducted in this arena. All of these are a challenge to do, but the latter can also be confusing and frustrating to patients who naturally want to maximize their odds of cure.

The confusion stems from the plethora of phase II and III trials that have been conducted in this setting, including hormones, vitamins, radiation, chemotherapy (standard and high dose), radioimmunoconjugates, immune therapy, vaccines, gene therapy, biologics, complementary medicines, and holistic approaches. The delivery is local, regional or systemic and may be relatively invasive and toxic. The frustration (for patients and health care providers) stems from the lack of clear benefit (survival), particularly when one of these "promising" strategies or modalities fails to achieve its anticipated effect when evaluated in formal randomized investigation. To date, the only randomized trial that has demonstrated a clear survival, albeit progression-free survival, advantage has been the GOG/SWOG 178 trial, which found significant improvement in this end point after an additional year of paclitaxel chemotherapy. Of note, 24% of patients randomized to the 12-cycle arm experienced clinical relevant neurotoxicity (grade II/III). The median gain to patients was 7 months and some authors have raised the question as to whether similar survival may be achieved by simply adopting a "wait and treat" policy.[1]

The current trial with oregovomab seems to follow suit with most other agents evaluated in this setting.[2-4] While unique and interesting in its mechanism of action, the primary objective was not reached. However, all is not lost in that, as is often the case, good clinical design has allowed for preliminary evaluation of other exploratory hypotheses. In the current trial, 2 important observations were discussed: mounting of individual human anti-mouse antibody (HAMA) titers and subgroup patient selection. In both of these cases, interesting findings have ushered development of follow-up protocols, which may allow

this immuno-targeted strategy to succeed in the treatment of advanced ovarian cancer. ■

Dr. Coleman is Associate Professor, University of Texas; MD Anderson Cancer Center, Houston

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CME Questions

2. **Docetaxel, administered weekly compared to every 3 weeks, has the advantage of:**
   a. better anti-tumor activitiy as measured by progression free survival and overall survival.
   b. less grade 3-4 neutropenia.
   c. less grade 3-4 asthenia
   d. Both (b) and (c)

3. **Combined modality (radiation and chemotherapy) was shown in the randomized trial from Memorial Sloan Kettering to offer which of the following advantages in patients with non-bulky Hodgkin's disease?**
   a. A better rate of complete remission
   b. A longer duration of complete remission
   c. Better overall survival at 60 months
   d. All of the above
   e. None of the above

4. **Using the Hyper-CVAD regimen as initial therapy for adults with ALL, investigators from MD Anderson demonstrated a CR rate, and a durability of CR at 5 years to be:**
   a. 92% and 68%.
   b. 92% and 38%.
   c. 68% and 38%.
   d. 38% and 5%.

5. **Ovarian autotransplantation was demonstrated by Hilders and colleagues from the Netherlands to be:**
   a. effective at preserving ovarian function for 6 weeks.
   b. effective at preserving ovarian function for 1 year.
   c. effective at preserving ovarian function for 8 years.
   d. technically impossible.

Answers: 2 (b); 3 (e); 4 (b); 5 (b)

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Statins and the Incidence of Rhabdomyolysis

The most commonly prescribed statins have a low incidence of rhabdomyolysis, according to the results a new study of more than 250,000 patients. Atorvastatin, pravastatin, and simvastatin were found have very low and virtually indistinguishable rates of rhabdomyolysis of 0.44 per 10,000 person-years (95% CI, 0.20-0.84). The data were obtained from 11 managed care health plans across United States from January 1, 1998, through June 30, 2001. Cerivastatin (Baycol-Bayer), which was withdrawn from the market in 2001, was found have a much of a higher rate of rhabdomyolysis, 5.34 cases per 10,000 person-years (95% CI, 1.46-13.68). The concomitant use of a fibrate with atorvastatin, pravastatin, or simvastatin was found to have increased the rate to 5.98 (95% CI, 0.72-216.0), while use of a fibrate with cerivastatin dramatically increased the rate to 1035 cases per 10,000 person-years of treatment (95% CI, 389-2117), or nearly 1 in 10. Older patients, especially those with diabetes, were found to have higher rates of rhabdomyolysis. The authors conclude that the most commonly prescribed statins have a low incidence of rhabdomyolysis, which is increased with the addition of a fibrate (*JAMA.* 2004;292:2585-2590).

The study confirms the safety of the most commonly used statins, but raises issues regarding the post marketing surveillance of cerivastatin. These concerns were addressed in a review in the same issue of *JAMA* regarding the potential conflict of interest once initial reports of rhabdomyolysis were reported to the company, and the delay in the availability of this information to consumers. The critique is accompanied by Bayer's rebuttal (*JAMA.* 2004;292:2622-2631, 2643-2646, 2655-2657, 2658-2659), which makes fascinating reading given the recent criticisms of the FDA and post marketing surveillance regarding coxibs.

A Crackdown on Importation of Drugs

Officials in both the United States and Canada are taking steps to crack down on the importation of prescription medications across the border. A New York District Court issued an injunction in December against Canada Care Drugs Inc., which gave the FDA authority to inspect the company to assure that they no longer import drugs to American consumers. The FDA had petitioned the court to take this action based on a sting operation run by the agency. FDA investigators purchased Neurontin and Sporanox through Canada

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com.

Care. Instead of Neurontin, investigators received APO-gabapentin and NOVO-gabapentin, formulations of the drug that are not subject to FDA scrutiny in this country. The Sporanox shipment included 84 tablets of the correct drug, but investigators felt that the amount was excessive, determining that patients should not take Sporanox continuously without checking with their physician. The court is scheduling a trial date for Canada Care, an action that is sure to put other Canadian importation companies on alert. Meanwhile, the Canadian government is also cracking down on Internet pharmacies that export drugs to the United States without evaluation by Canadian doctors. The government is considering making it illegal for Canadian doctors to countersign prescriptions from other countries. This move in Canada is prompted by concern over shortages of drugs for Canadian citizens, especially given threats by American drug companies to withhold additional shipments of drugs to Cananda, where they have strict price controls, knowing that many of these drugs may come back to the US market were there are no price controls. These moves are strongly supported by PhRMA, the powerful pharmaceutical advocacy group.

FDA Actions

The FDA has approved a new non-benzodiazepine hypnotic for the treatment of insomnia. Sepracor, a company that specializes in marketing active isomers of currently approved drugs, has received approval to market eszopiclone, the active (S)-isomer of zoplicone, which is available outside the United States. The drug is similar to zopidem (Ambien) and zaleplon (Sonata) in that it has a lower incidence of tolerance, dependence, and withdrawal symptoms than benzodiazepines. Based on a 6-month, double-blind, placebo-controlled safety and efficacy trial, the FDA decided not to limit eszoplicone's indication to short-term use. Eszoplicone will be available in 1mg, 2mg, and 3mg tablets, and will be marketed in United States under the trade name Lunesta. Sepracor is also studying the drug for treatment of insomnia in patients with depression or pain, and in peri-menopausal women.

Novartis has received approval to market darifenacin extended release tablets for the treatment of overactive bladder with symptoms of urging incontinence, urgency, and frequency. The drug is an M3 (muscarinic) receptor blocker that increases urinary capacity and decreases urinary episodes and frequency of incontinence, along with feelings of urgency. Darifenacin, which is already available in Europe, will be marketed in the United States as Enablex.

Drugs approved under the FDAs accelerated approval program are often approved on the basis of surrogate end points, such as tumor markers that would indicate the likelihood of clinical benefit. The FDA, however, requires that cancer drugs in particular, must document clinical benefit in subsequent studies to remain marketable. A recent case-in-point is AstraZeneca's gefitnib (Iressa), which was approved for treatment of non small cell lung cancer in patients who failed other courses of cancer therapy. A recent study of gefitnib involving nearly 1700 patients failed to show a survival benefit better than placebo. The drug, which was initially approved in 2003, now faces a FDA review to determine whether the drug will be removed from the market. In a letter to physicians, AstraZeneca "urges you to consider other treatment options in recurrent non small cell lung cancer patient population." In the meantime, Genentech and Roche's erlotinib (Tarceva), which has shown survival benefit for the same patient population, remains a viable option.

The FDA has issued a Public Health Advisory regarding the use of anti-inflammatories including COX-2 inhibitors because of recent indications that the drugs may increase the risk of cardiovascular disease and stroke. The agency is requiring evaluation of all prevention studies that involve the COX-2 inhibitors celecoxib (Celebrex) and valdecoxib (Bextra) to ensure that adequate precautions are in place. Several prevention studies regarding potential benefit of these drugs on colon polyps and Alzheimer's disease are either in progress or planned in the near future. Meanwhile, the agency is recommending that physicians should prescribed Celebrex or Bextra with caution, particularly in patients at risk for cardiovascular disease, and should weigh the risk vs benefits.

The FDA is also recommending that consumers should use over-the-counter anti-inflammatories in strict accordance with the label directions, taking them for no longer than 10 days without consulting a physician. ■