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INSIDE

Prospective Phase II Results of Chemoradiation for Merkel Cell Carcinoma are Encouraging

ABSTRACT & COMMENTARY

Synopsis: *Merkel cell carcinoma is a tumor of the skin that is well known for its metastatic potential. Because of its scarcity, no trials have been reported. Poulsen and colleagues from Australia conducted a unique multi-institutional Phase II prospective trial of concomitant chemoradiation for patients with high-risk disease and concluded that their regimen resulted in disease control and survival rates that are better than those reported in the literature.*

Source: Poulsen M, et al. *J Clin Oncol*. 2003;21:4371-4376.

POULSEN AND ASSOCIATES IN AUSTRALIA CONDUCTED A prospective Phase II trial using chemoradiation for primary, adjuvant, or salvage therapy of merkel cell carcinoma (MCC). They based their approach on the similarities in natural history and biologic behavior between MCC and small-cell lung cancer. The study, which was carried out between 1996 and 2001, accrued 53 patients with high-risk disease from 6 institutions. High risk was defined as primary tumor > 1 cm, presence of lymphvascular invasion, involved lymph nodes (Stage II), subtotal resection, or local recurrence following surgery. Patients with low-risk disease, poor performance status, or distant metastases were excluded. Surgery was frequently performed prior to referral to the oncology department. Clear margins were not mandatory. Median age was 67 years (range, 43-86 years). There were 41 patients with primary disease (77%) and 12 with recurrences (23%). Forty-two percent (n = 22) of the MCC lesions were on the head and neck, 30% (n = 16) were at the extremities, 24% were occult primary tumors with disease in the lymph nodes (n = 13), and 4% were located on the trunk (n = 2). Seventy-two percent (n = 38) were treated adjuvantly, and 28% (n = 15) were treated with primary chemoradiation. Among the patients who underwent surgery, 28/53 (53%) achieved clear margins. Sixty-two percent of patients (n = 33) had involved N1 and/or N2 lymph nodes.

For those patients treated adjuvantly, the median interval from surgery to chemoradiation was 47 days (range, 14-87). The radia-

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tion therapy portals included the primary tumor or tumor bed with a 3-5 cm margin and lymph nodes located < 20 cm away. Dose was 50 Gy in 25 fractions (range, 44-60 Gy) over 5 weeks to the operative bed or gross disease and 45 Gy in 25 fractions to areas of suspected microscopic disease. Four cycles of chemotherapy were administered, with the option to continue chemotherapy beyond the fourth cycle. Chemotherapy was given on weeks 1, 4, 7, and 10, with the latter 2 cycles given after the end of the RT. The carboplatin dose was calculated according to the Calvert formula, and etoposide was given at 80 mg per square meter.

Outcomes were measured from the start of chemoradiation. Median follow-up was 48 months (range, 11-70 months). No patients were lost to follow-up. Eighty-three percent of patients received RT per protocol, with no unacceptable major deviations, and 87% completed all 4 cycles of chemotherapy. Sixty-four percent (n = 34) of patients suffered Grade 3 or 4 skin reactions (4 with Grade 4), and 35% experienced febrile neutropenia (n = 19). Grade 3 or higher late skin toxicity occurred in 15% at 3 years. Three-year overall survival was 76%, 3-year disease-free survival was 65%, and 3-year actuarial local control was 75%. Local control was 77% for patients treated adjuvantly and 71% for patients receiving primary chemoradiation (*P* value not given). The crude 3-year distant metastatic rate was 17% (n = 9).

On multivariate analysis, age, lymph node status, disease site, and presence of gross disease were evaluated. Lymph node status was significant in terms of overall survival (*P* = .001) but not local control. Lesions on the lower extremities did statistically significantly worse (*P* = .002), and the presence of gross disease at treatment was not a significant factor for overall survival.

Poulsen et al concluded that chemoradiation was tolerable for the majority of MCC patients and that the survival and disease control rates demonstrated in their study appeared to be superior to other reported series. They suggested that any delay in chemoradiation in order to perform further surgery (eg, to obtain clear margins) would be detrimental to treatment efficacy. They also suggested that the low rate of distant metastases seen in this trial is consistent with a positive influence exerted by the chemotherapy. However, given the heterogeneity of the high-risk patients treated, Poulsen et al advised great caution in interpreting their results. They are now considering a Phase III trial comparing chemoradiation with carboplatin and RT followed by carboplatin/etoposide as the experimental arm, vs radiotherapy alone as the standard arm, recognizing that febrile neutropenia was their worst toxicity.

COMMENT BY EDWARD J. KAPLAN, MD

The issue of adjuvant therapy for MCC remains controversial. Many studies have advocated postoperative radiotherapy following resection of MCC.[1-3] Fenig et al from Israel published one of the only papers addressing combined modality therapy for MCC, using a sequential approach with surgery or chemotherapy followed by RT.[4] In the largest retrospective study on MCC reported to date, investigators from MSKCC published their findings on 102 MCC patients treated between 1969 and 1996.[5] Very few patients received adjuvant therapy, either with RT or with chemotherapy. The most common site of recurrence was in regional lymph nodes, which were affected in 40/55 recurrences (73%). Median follow-up was 35 months, 5-year overall survival was 76%, and 5-year disease-free survival was 74%. Based on these results, the authors recommended an aggressive approach toward the treatment of clinically negative lymph nodes. Poulsen et al were presumably motivat-

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ed by this type of recommendation, with impressive results. First, they organized a trial for a rare disease, and second, they managed an annual accrual rate nearly 3 times that in the MSKCC paper. Comparing the 65% 3-year DFS from Poulsen's group to the 74% 5-year DFS from MSKCC seems to reflect an advantage in favor of the MSKCC data, until one factors in that every one of the Australian patients had high risk disease. Looking at it from that perspective, the chemoradiation data begin to look rather good. The very low rate of DM seen in the Australian trial is particularly striking given that almost two-thirds of the patients in that study had positive lymph nodes, compared with the 9-33% reported elsewhere in retrospective studies, including the 22% cited in the MSKCC study.

Further efforts are necessary to amplify upon these early results, while at the same time improving upon the toxicity profile. The Australian team is contemplating a randomized trial, and they indicated that they would likely solicit international cooperation. Hopefully, not only will their perseverance lead to higher cure rates for MCC, but their work can serve as an inspiration to others in the development of trials for other rare tumor types. ■

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Irinotecan in Patients with Hepatic or Renal Dysfunction or with Prior Pelvic Radiation

ABSTRACT & COMMENTARY

Synopsis: *Patients with elevated bilirubin treated with irinotecan have an increased risk of toxicity, and a dose reduction is recommended. Patients with elevated AST, creatinine or prior pelvic radiation do not appear to have increased sensitivity to irinotecan, but the data are not adequate to support a specific dosing recommendation.*

Source: Venook, et al. *Ann Oncol*. 2003;14:1783-1790.

Irinotecan (CPT-11; 7-ethyl-10-[4(-1-piperidino)-1-piperidino] carbonyloxy camptothecin) is a semi-synthetic derivative of the natural alkaloid camptothecin. It is a prodrug that belongs to the class of antineoplastic agents called topoisomerase I inhibitors. In vivo, irinotecan is converted by carboxylesterases to its most active cytotoxic metabolite, 7-ethyl-10-hydroxy-camptothecin (SN-38), which exerts its cytotoxicity by generating intermediate forms of drug-stabilized covalent DNA, topoisomerase-I complexes. It has been used primarily in the treatment of metastatic colorectal cancer but also has activity in non-small-cell lung cancer. It can be administered singly in either a weekly or 3-week schedule and is often combined with leucovorin and 5-fluorouracil. The dose-limiting toxicities of irinotecan are diarrhea and myelosuppression. Diarrhea appears to be due to intraluminal exposure to SN-38, although it is controversial as to the importance of biliary excretion of SN-38 vs intraluminal formation by beta glucuronidases. Aggressive early intervention with loperamide can reduce the severity of the toxicity. There has been concern over the toxicity of this agent, particularly when combined with fluoropyrimdines and in patients with hepatic and renal dysfunction. This was in part due to the biliary index, which has been demonstrated to correlate with the severity of diarrhea on the weekly schedule.[1] There also has been concern for the dosing of irinotecan in hepatic dysfunction, since many patients with metastatic colorectal cancer may have extensive liver metastases. The Cancer and Leukemia Group B has conducted trials with paclitaxel and gemcitabine in patients with end organ dysfunction.[2,3] Therefore, the current trial was initiated.

■ COMMENT BY STUART M. LICHTMAN, MD, FACP

A Phase I type study design was used. Adult patients with biopsy proven solid tumors or lymphomas that were refractory to standard therapy or for which no standard therapy existed were eligible for the study. Patients were assigned to 1 of 4 treatment cohorts: I, aspartate aminotransferase (AST) $\geq 3 \times$ upper limit of normal and direct bilirubin < 1.0 mg/dL; II, direct bilirubin 1.0-7.0 mg/dL; III, creatinine 1.6-5.0 mg/dL with normal liver function; or IV, prior pelvic XRT with normal liver and renal function. The starting dose for patients in cohorts I, III, and IV was 225 mg/m^2 and cohort II 145 mg/m^2 by 90-min infusion every 3 weeks. One cycle consisted of 2 treatments. Three patients were accrued to each dose level. If none of these 3 patients experienced dose-limiting toxicity, the dose was to be increased in subsequent groups to a maximum of 350 mg/m^2. Pharmacokinetic analyses were performed.

Thirty-five patients were enrolled in the study. Twenty-nine patients had received prior chemotherapy. Metastatic gastrointestinal cancer was the underlying disease in 13 patients, 8 of the patients had primary liver cancer and 9 patients had genitourinary cancers. The CALGB performance status was 0-1 in all but 5 patients. Seven patients encountered a dose limiting toxicity during the first cycle; 5 of the 7 had prior chemotherapy, and 2 had prior radiotherapy. The most common dose limiting toxicity (DLT) was neutropenia, seen in 4 patients, which manifested as nadir counts rather than protracted neutropenia. In cohort II, 2 of the DLTs were neutropenia in patients with baseline direct bilirubins of 4.5 and 1.5 mg/dL, respectively, and the other DLT was worsening liver function in a patient with a baseline direct bilirubin of 1.4 mg/dL. The 2 patients with DLT in the renal dysfunction cohort had grade 4 diarrhea and neutropenia with calculated creatinine clearances of 36 and 32 mL/min, respectively. No patient who had a DLT was re-dosed with irinotecan.

There were no significant differences in the pharmacokinetic parameter estimates for irinotecan or its metabolites between patients with renal impairment and those with prior radiotherapy. In comparison, patients in cohort II had significant, clinically relevant decreases in irinotecan clearance. Irinotecan clearance was estimated to be reduced by 35% in cohort II compared with cohorts III and IV. A large variability within the cohort groups prevented detection of significant differences in the fraction of the parent compound metabolized among cohorts. Systemic exposure was similar across the cohorts.

This study was designed to make the dosing of chemotherapy in the patients with organ dysfunction a more precise exercise. It has long been one of empiricism. With the heterogeneity of the population studied precise dosing recommendations could not made. It was determined that patients with elevated direct bilirubin should be treated with irinotecan at reduced doses. The dosing in patients with renal dysfunction could not be determined as no patients with creatinines above 3.5 mg/dL were evaluated and the doses used were less than the standard every 3-week dosing.[4] This study was based on a 3-week dosing schedule and it is uncertain whether it can be extrapolated to combination therapies are those used weekly. However, the results of the study are a reminder that the data generated in early Phase I or II trials are not generalizable to patients with organ dysfunction. ■

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Gemcitabine and Oxaliplatin Combinations for Patients with Hepatocellular Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Hepatocellular carcinoma is one of the most common malignancies worldwide, and, for those with advanced disease, treatment responses have been dismal. The current report of a trial of gemcitabine and oxaliplatin offers some hope. Using 2 different schedules of these agents, this study found an approximate 20% objective response rate with stable disease occurring in an additional 50%. The combinations were well tolerated, with Grade 3 hematotoxicity occurring in approximately one-third, but there was no severe hematologic or non-hematologic toxicity, including no cases of Grade 3 or 4 neurotoxicity.*

Source: Taieb J, et al. *Cancer*. 2003;98:2664-2670.

Hepatocellular carcinoma (HCC) is among the most common tumors worldwide, yet effective treatment remains elusive. In the current report from France, 2 different schedules of gemcitabine and oxaliplatin were examined prospectively in a total of 21 patients with HCC. Eleven patients received gemcitabine 1000 mg/m^2, as an infusion of 10 mg/m^2 per minute (total of 100 minutes/m^2) on Day 1, followed by oxaliplatin 100 mg/m^2 as a 2-hour infusion on Day 2 (GEMOX-1 regimen). Ten subsequent patients received same-day therapy with gemcitabine 1500 mg/m^2 as a 30-minute infusion followed by oxaliplatin 85 mg/m^2 as a 2-hour infusion (GEMOX-2). Treatments were repeated every 2 weeks, and doses were adjusted if Grade 3-4 toxicity occurred. If Grade 3 oxaliplatin neurosensitivity developed, the drug was discontinued and patients continued with gemcitabine as a single agent. Patients who responded or had stable disease received the full treatment for at least 4 months. Treatment was discontinued in patients with progressive disease, repeated Grade 3-4 toxicity, or with treatment refusal.

Patients were recruited onto study for a 6-month period, 10 patients were receiving initial chemother-

apy, and 11 had previously been treated and progressed on a different chemotherapy regimen. Several of the patients had hepatitis B or C infections, and some had a history of heavy alcohol use. Underlying cirrhosis was present in 18 of the 21 patients. These characteristics were balanced with regard to those treated with the GEMOX1 vs GEMOX2 schedules.

The overall response rate was 19% (95% CI, 13-26%). Ten patients (48%) had stable disease and 7 patients (33%) had progression. Responses lasted from 4 to 8 months, and the median progression-free survival was 5 months and overall survival, 12 months. There were no differences in overall survival or progression-free survival were between the 2 treatment groups. Among the 16 patients with initially elevated AFP levels, the level fell by > 50% during therapy in 9 patients. Among the 15 patients with an initial performance status of > 0, 8 patients (53%) exhibited improvement during treatment. Weight gain (without edema or ascites) was observed in 8 patients and pain, ascites appetite and asthenia improved in 6 of 10 patients who were initially symptomatic. The median time to symptom improvement was 6 weeks.

Grade 3-4 toxicity occurred in 8 patients, with hematological toxicity being most common. There were no treatment-related deaths and no episodes of febrile neutropenia. No Grade 3 neurotoxicity was observed. Comparing GEMOX-1 with GEMOX-2, there was no significant difference in antitumor efficacy, but GEMOX-1 was tolerated better.

COMMENT BY WILLIAM B. ERSHLER, MD

The prior experience with chemotherapy for HCC has been discouraging. Accordingly, even the modest findings reported seem like a ray of sunshine. Measurable, sustained improvement in 19% and stable disease in close to 50% compares favorably to any other published experience, especially when considering that more than half of the patients had progressed on prior chemotherapy. Furthermore, the toxicity profile was reasonable, and dose reductions and delays were infrequent. Other chemotherapy regimens have included 5-flurouracil, cisplatin, and doxorubicin with response rates varying 5-25% but with significant toxicity.[1-3] In one recently reported trial, there was a 0% objective response rate with either single-agent doxorubicin or nolatrexed.[4] Similarly, Phase II studies of other agents, including paclitaxel, irinotecan, and topotecan have yielded discouraging results.

Thus, the combination of gemcitabine and oxaliplatin offers a promising new approach to the management of this difficult tumor. Additional, larger-scale trials are needed to establish the optimal dosing and scheduling of these agents and to determine if there are predictive factors that would indicate likely treatment response.

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21 Years Later: Adjuvant Hormonal Therapy for Elderly Breast Cancer Patients

ABSTRACT & COMMENTARY

Synopsis: *In an adjuvant breast cancer trial conducted more than 20 years ago, older patients were randomized to treatment with tamoxifen and prednisone or no adjuvant therapy. Now, at 21 years of follow-up, it is clear that disease-free and overall survival remain better for those who received treatment. Current practice, however, uses a more protracted course of tamoxifen, and it is possible that long-term results for older patients under treatment may reflect a larger number of adverse outcomes.*

Source: Crivellari D, et al. *J Clin Oncol*. 2003;21:4517-4523.

Breast cancer occurs most commonly in older women, and it is currently observed more frequently in early stages. Yet, the matter of adjuvant therapy remains unsettled for this age group. In the current report, the data from the International Breast Study Group (Trial IV) after 21 years of follow-up is presented. This multi-institutional trial, which was conducted from 1978 to 1981, randomized lymph node-positive patients, aged 66-80, who were randomly assigned to treatment with tamoxifen plus low-dose prednisone (p+T) or no adjuvant therapy. Of the 349 enrolled, there were 329 evaluable patients. Demographic characteristics were equally divided in the 2 treatment groups.

After a median follow-up of 21 years, a single year of p+T significantly prolonged disease-free survival (DFS; $P = .003$) and overall survival ([$P =$

.05]; 15-year DFS, 10% ± 3% vs 19% ± 3%; hazard ratio, 0.71; 95% CI, 0.58-0.86). The DFS advantage was seen for patients in the following subpopulations; 1-3 positive nodes (P = .04), 4 or more nodes (P = .04), ER-positive patients (P = .02), patients with unknown ER status (P = .009), tumor size > 2 cm (P = .03), age 66-69 years (P = .01), and age 70-80 years (P = .04) but not separately for ER-negative and smaller tumor size subgroups.

When comparing competing causes of failure (breast cancer recurrence and deaths before breast cancer recurrence), p+T was far superior in controlling breast cancer recurrence (P = .0003), but the improvement was seen mainly in soft-tissue sites. Conversely, patients in the p+T group were more likely to die before a breast cancer recurrence (P = .03).

COMMENT BY WILLIAM B. ERSHLER, MD

Such long-term success of adjuvant therapy in elderly breast cancer patients had not been previously reported. Data from the same study were published at a median follow-up of 8 years,[1] and it is encouraging to find the initial positive results were sustained. In 1978 when this trial was initiated, the optimal duration of therapy was unclear and a concurrent ECOG trial (examined 2 years of tamoxifen vs placebo in a similar population of patients) also resulted in favorable early findings.[2,3] Most consensus guidelines currently recommend a 5-year course of tamoxifen for node-positive ER+ patients.[4,5] The long-term results for older patients treated in this manner may demonstrate that deaths from causes other than breast cancer are increased, presumably due to increased thromboembolic disease associated with tamoxifen treatment, for which the elderly appear particularly susceptible (ref30). However, such may not be the case with the equally effective, but less toxic aromatase inhibitors.[6]

Thus, tamoxifen has been shown to enhance disease free and overall survival, even when administered for 1 year only (with prednisone) in elderly node positive patients. It is probable that more sustained treatment (eg, 5 years) will also have a positive effect on long-term outcomes, but these will have to be balanced with a likely increase in encountered adverse events. ■

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Uterine Papillary Serous Carcinoma: Comparisons of Outcomes in Surgical Stage I Patients With and Without Adjuvant Therapy

ABSTRACT & COMMENTARY

Synopsis: *In this largest reported series of surgical Stage I UPSC patients, recurrence rates were lower than those published in previous studies, suggesting a potential benefit of comprehensive surgical staging in these patients. The risk of recurrence and the mean overall survival were similar between surgical Stage I UPSC patients who were managed conservatively and those treated with adjuvant radiation therapy. These data question the benefit of radiation therapy in UPSC patients with disease confined to the uterus. Finally, given the absence of recurrences and disease-related deaths for adjuvant chemotherapy in these patients, a Phase II/III trial evaluating adjuvant chemotherapy in surgical Stage I UPSC patients should be considered.*

Source: Huh WK, et al. *Gynecol Oncol*. 2003;91(3): 470-475.

In a collective effort from the tumor registries of 4 academic centers, Huh and colleagues accessioned cases of uterine papillary serous carcinoma (UPSC), which, following comprehensive surgical staging, were identified with disease limited to the uterine corpus—surgical stage I. The retrospective data set, conducted for a 14-year period ending in 2000, was collected to address the benefit, if any, from the use of adjuvant therapy. Surgical staging required removal of the uterus, tubes, and ovaries, peritoneal cytology, and pelvic and paraortic lymphadenectomy. Specific biopsy of other peritoneal tissue and organs were not required but were obtained in some cases. In all, 60 patients were identified, 40 of whom were simply observed following surgery. The remaining 20 received adjuvant radiation therapy (n = 12), chemotherapy (n = 9) or both (n = 1). Recurrence rates were no different between those patients receiving adjuvant therapy (16%) and those

undergoing conservative observation (17%). Interestingly, no recurrences were observed in patients receiving chemotherapy—all of whom remain alive at a mean 32 months. The 5-year disease-free and overall survival rates for the observation group were 65% and 66%, respectively. This compared to the 5-year disease-free and overall survival rates of 60% and 59%, respectively, for those patients receiving radiation therapy. The small differences were not statistically different.

Huh et al conclude that performance of comprehensive surgical staging most likely contributed to the lower than expected historical recurrence rates. However, despite a noted risk for distant failure, no clear benefit from adjuvant radiation therapy was obvious. The lack of disease failure in patients receiving chemotherapy is interesting and should herald further clinical investigation.

COMMENT BY ROBERT L. COLEMAN, MD

Since its initial description more than 20 years ago, UPSC has been a challenging clinical entity. Characterized by frequent extrauterine spread, aggressive clinical behavior, and inconsistent preoperative histology, this distinct uterine cancer is uncommon (about 4-9% of all uterine primaries) but remains poorly understood. Effective therapeutic strategies are elusive and, as appreciated in this study, even candidate selection for therapy is controversial. What is well documented and what makes management decisions so difficult is that its natural history appears to be very different from the much more common uterine endometrioid cancer. Surgical care and adjuvant therapy, which has been traditionally applied under the supposition of parity with the more common endometrioid histology has, to some degree, limited our ability to make accurate decisions about management—particularly with the retro-spectroscope. Since early stage disease represents the most curable cohort in all histologic subgroups, identifying the most effective adjuvant treatment, if any, is a premium target.

There are several notable differences between UPSC and uterine endometrioid adenocarcinoma that help to illustrate the clinical challenges faced. First, the diagnosis is variably determined by standard endometrial aspiration. Studies have noted that between 37% and 77% of preoperative biopsies are representative of the final histology in cases of UPSC. Some of this discrepancy may be explained by the occurrence of a mixed pattern in up to 40% of patients.

Unfortunately, the appearance of endometrioid features does not appear to alter the clinical course. Second, the patient demographic is generally one of an older population (median age, 68) and generally not obese or peripherally exposed to exogenous estrogen. Third, local recurrence is frequently associated with not only intra-abdominal and distant disease but also death. In a trial of endometrioid adenocarcinoma, Stage I patients who, following observation, were identified with local recurrence, treatment with radiation was associated with successful salvage in nearly 50% at 4 years. Fourth, little apparent relationship exists between myometrial invasion and the occurrence of extrauterine disease.

While the depth of myometrial invasion in UPSC patients has been determined by some to be an independent prognostic factor, up to 40% of patients with non-invasive UPSC will have evidence of extrauterine and frequently intra-abdominal metastatic disease. This latter observation is likely responsible for the seemingly improved prognosis of Stage I patients reported in this and other contemporary trials. "Stage migration" refers to the temporal reclassification of a particular cohort of patients on the basis of diagnostic precision—or in this case, on the basis of occult disease re-categorizing Stage I patients to a higher stage—a classic example of, ". . .if you look for it, you will find it." In this regard, the current recommendation for proper staging of a patient with UPSC is to obtain additional intra-abdominal biopsies similar to those performed for ovarian cancer.

The study by Huh et al attempts to shed light on the management of properly evaluated (for the most part) Stage I UPSC. The goal of the paper was to elicit the proper management of those patients in whom no extrauterine disease was identified, knowing that our clinical "track record" with this disease is poor and frequently characterized by distant failure. Although no "winning" strategy was declared in the retrospective data set, important contributions were made in the observations that adjuvant radiation therapy did not improve any of the survival parameters and in the curious absence of recurrence in patients given adjuvant chemotherapy. Although the number of patients in this subgroup was small (n = 7), the 32-month mean follow-up was consistent with the other subgroups; a plea for prospective clinical trials is certainly supported.

The role of chemotherapy in endometrial cancer has gained new import following the presentation of the results from a randomized trial in advanced-stage endometrial cancer (GOG 122). In this trial, adriamycin and cisplatin were compared against whole abdominal radiation in Stage III and IV uterine cancer patients. Significant reduction in the hazard for recurrence (0.68, 95% CI, 0.52-0.89) and death (0.66, 95% CI, 0.5-0.89) was observed with the more toxic chemotherapy regimen. Modification to both the chemotherapy and radiation protocols is currently being investigated through a randomized trial in similar cohort of patients.

Given the rarity of UPSC and the limited number of Stage I patients to study, answers to these important issues will be some time off. However, identification of the uniqueness of this histology is an important first step. In the meantime, treatment recommendations will be based on the extrapolation of active therapies in other cohorts that address the characteristic natural history of UPSC. ■

Dr. Coleman is from the Department of Gynecologic Oncology, University of Texas Southwestern Medical Center, Dallas, Tex.

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CME Questions

7. For the treatment of hepatocellular carcinoma, the combination of gemcitabine and oxaliplatin was shown:

a. to produce complete remissions in 45% of cases.
b. to result in objective responses in approximately 20% of patients.
c. to have an objective response rate of 5%, but a subjective response rate, including improved quality of life in approximately 20%.
d. to be less effective than single agene doxorubicin.

8. Treatment with tamoxifen and prednisone has been shown, after a median of 21 years, to have enhanced disease free and overall survival for all but which of the following subgroups of elderly (age 66-80) patients?

a. Those with ER+ tumors
b. Those with ER- tumors
c. Those with primary lesions of < 2 cm
d. Those with primary lesions of > 2cm

Answers: 7 (b); 8 (b)

In Future Issues:

More on Lymphoma Treatment in the Elderly

PHARMACOLOGY WATCH

Valacyclovir Reduces Genital Herpes Transmission

A once-a-day dose of a valacyclovir reduces the rate of transmission of genital herpes (HSV-2) from an infected partner to an uninfected susceptible partner, according to a new study. The study group included 1484 immunocompetent, heterosexual, monogamous couples in which 1 partner had symptomatic genital HSV-2 and the other was susceptible to HSV-2. The infected partners were randomized to valacyclovir 500 mg once daily or placebo for 8 months. At the end of the study period, clinically symptomatic HSV-2 infections developed in 4 of 743 susceptible partners in the valacyclovir group vs 16 of 741 in the placebo group (HR, 0.25; 95% CI, 0.08-0.75; $P = 0.008$). Overall acquisition of HSV-2, including asymptomatic infections, was observed in 14 partners in the valacyclovir group compared to 27 in the placebo group (HR, 0.52; 95% CI, 0.27-0.99; $P = 0.04$). Valacyclovir significantly cut down on viral shedding in the infected partner and also significantly cut down on the rate of HSV-2 outbreaks in the infected partner. The authors caution that 37% of couples in the study did not use condoms even though counseled to do so, and that condom use and abstinence during attacks are the most effective methods of preventing transmission (*N Engl J Med*. 2004;350:11-20).

Erythropoietin Safe for Cancer Patients?

A fascinating news item published in the December 17 issue of *Journal of the National Cancer Institute* raises the question of whether erythropoietin is safe to use in cancer patients. According to the news report, several studies suggest that many cancer cells have erythropoietin receptors that may be stimulated by erythropoietin injections. Erythropoietin is commonly given to cancer patients to treat chemotherapy-related, or cancer-related anemia. Two recent trials have shown that erythropoietin use is associated with decreased survival in some cancer patients according to the news report. Erythropoietin receptors have been found on head and neck cancer cells, prostate cancer cells, and ovarian cancer cells, as well as breast, renal, and uterine cancer cells. Preliminary data suggest that some of these cancers may actually proliferate in the presence of erythropoietin. The association between erythropoietin and decreased survival for some cancer patients needs further evaluation (*J Natl Cancer Inst*. 2003;95:1820-1821).

WHI, ALLHAT Trials Still Spur Research

It appears that 2 landmark studies have significantly changed practice patterns in this country. The Women's Health Initiative (WHI) study published in July 2002, and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) published in April 2000 both showed negative results with some of the most widely prescribed pharmaceuticals in this country. WHI suggested that combined estrogen/progesterone increases the risk of breast cancer and cardiovascular disease in postmenopausal women. Researchers from Stanford looked at prescription trends in hormone therapy from 1995 to July 2003. Annual hor-

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mone therapy prescriptions increased dramatically between 1995 in 1999 and then remained stable through June 2002. Following publication of the WHI in July 2002, prescriptions for Prempro, the combination estrogen/progesterone used in the study, declined by 56%. New prescriptions for conjugated estrogen also declined significantly. Small increases were seen with topical estrogens and low-dose estrogen preparations over the same time period (*JAMA*. 2004;291:47-53). ALLHAT was terminated early and the results released in December 1999, and published in April 2000 because early results showed that doxazosin, an alpha-blocker, was significantly inferior to diuretics with respect to preventing stroke, congestive heart failure, and a composite of other cardiovascular outcomes. The same group from Stanford reviewed alpha-blocker prescription trends from 1996 to 2002. Steady increases in alpha-blocker prescriptions were seen in between 1996 and 1999, but new prescriptions for the drugs declined 26% between 1999 and 2002. Changes in pricing, generic version, drug promotion, or competition did not have a confounding effect. The authors conclude that modest declines in alpha-blocker prescribing were seen after publication of ALLHAT (*JAMA*. 2004;291:54-62).

Alpha-Blockers Useful in BPH Treatment

Alpha-blockers are useful in treatment with benign prostatic hyperplasia (BPH). Now a new study shows that the combination of the 5-alpha-reductase inhibitor finasteride (Proscar) with an alpha-blocker may be superior to either drug alone in treating BPH. Researchers randomized 3047 men to placebo, doxazosin, finasteride, or combination therapy with the end point of clinical progression of BPH. Clinical progression was defined as an increase in the American Urologic Association symptom score of these 4 points, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection. Both doxazosin and finasteride significantly reduced clinical progression (doxazosin-39% risk reduction, $P < 0.001$; finasteride 34% risk reduction $P = 0.002$) compared to placebo. The combination of doxazosin and finasteride however resulted in a 66% risk reduction compared with placebo ($P < 0.001$). Mean follow-up was 4.5 years. The authors conclude that long-term combination therapy with doxazosin and finasteride was safe and significantly reduced the risk of clinical progression of BPH and was superior to either drug alone (*N Engl J Med*. 2003;349:2387-2398).

T4 Alone is OK for Hyperthyroidism Therapy

Hypothyroidism is one of the most common clinical disorders in general practice. Controversy about replacement therapy has raged for years regarding the need for liothyronine (T3) in addition to thyroxine (T4). A new study from Bethesda suggests that thyroxine alone is optimal therapy. In this randomized, double-blind, placebo-controlled trial, 46 hypothyroid patients were randomized to their usual dose of levothyroxine, or combination therapy in which their dose of levothyroxine was decreased by 50 µg/d, and liothyronine 7.5 µg was given twice daily for 4 months. TSH levels were followed and remained stable throughout the study. The main outcomes were scores on the hypothyroid specific health-related quality of life questionnaire, body weight, serum lipid levels, and 13 neuropsychological tests before and after treatment. After 4 months, body weight and serum lipid levels were unchanged in both groups. Quality of life scores improved in both groups (23% improvement levothyroxine group [$P < .001$], 12% improvement combination group [$P = .02$]). There is no statistical difference in neuropsychological testing between the 2 groups except for better performance in the Grooved Peg Board test in the levothyroxine group. The authors conclude combination therapy with levothyroxine plus liothyronine offers no advantage over single therapy with levothyroxine for the treatment of hypothyroidism (*JAMA*. 2003;290:2952-2958).

FDA Ban on Ephedra Awaits Final Ruling

The FDA has issued a consumer alert, banning the dietary supplement ephedra. The ban will become effective 60 days after the publication of a final rule stating that dietary supplements containing ephedra represents an unreasonable risk of illness or injury. This unprecedented move, the first time the FDA has banned a supplement, comes after several high-profile deaths linked with ephedra including professional athletes. Overall, the FDA has reports of 155 deaths associated with ephedra and more than 16,000 complaints. The drug is commonly used for weight loss and is present in many over-the-counter preparations. It is also widely used in Chinese herbal medicine practices, where it is known as Ma huang, and has been a staple of therapy for thousands of years for a variety of ailments including asthma and fever. The FDA has allowed an exemption for practitioners of Chinese medicine as long as is not used in high dose for weight loss. ■