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Transperineal Interstitial Photodynamic Therapy for Prostate Cancer

ABSTRACT & COMMENTARY

Synopsis: *Salvage therapy options for locally recurrent prostate cancer following radiotherapy failure include radical prostatectomy, brachytherapy, and cryotherapy. This study describes the results of the first effort at implementing percutaneous transperineal interstitial photodynamic therapy (PDT) and concludes that local control may be achievable with PDT if better light dosimetry is developed.*

Source: Nathan TR, et al. *J Urol*. 2002;168:1427-1432.

Between 1996 and 1999, Nathan and colleagues at the University College London Hospitals enrolled 14 patients in a Phase I-II study to assess the safety and efficacy of percutaneous interstitial photodynamic therapy (PDT) for local failures following radiotherapy for prostate cancer. Patients were identified for the study based on 2 or more consecutive rises in PSA at follow-up, and eligibility was confirmed based on a positive biopsy. No patient was suitable for surgery. Patients with "locally advanced" or extraprostatic disease were excluded. Median age was 70 years (range, 58-77). Median time from radiotherapy was 42 months (range, 22-108).

Each patient was given 0.15 mg/kg of meso-tetrahydroxyphenyl chlorin, a photosensitizer, intravenously. Following 3 days under low lighting, a series of 2-8 15-cm, 19-gauge needles was placed transperineally under MRI or ultrasound guidance with the patients under sedation. Depending upon the location of the positive biopsies, 1 or both prostate lobes were targeted. Since this study was the first attempt at applying this technology in humans to kill cancer, no attempt was made to treat the entire gland. The peripheral zone of the affected lobe was treated from base to apex at 1-cm intervals up to 4 positions per needle as each needle was withdrawn. A median of 4 laser fibers (range, 2-8) was used per patient. A diode laser was used to deliver 652-nm red light along 0.4-mm diameter laser fibers. In an effort to proceed cautiously, the first 5 patients received 20 J light dose based on earlier canine experiments. Four of these initial

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5, along with 9 more patients, were then treated with "at least 50 J." Some poor responders underwent repeat treatment. Only results from the higher light dose were reported.

Follow-up biopsies were obtained several days after treatment and again at 1-4 months post-PDT. Serial PSA and MRI or CT scans were done a few days after treatment and again at 2 months. Flexible sigmoidoscopy was done pretreatment and 2-5 days posttreatment.

PSA levels dropped in 9 of the 13 patients treated, and 5 patients had negative post-PDT biopsies. Two patients maintained undetectable PSA levels, the longest being 26 months. Post-PDT CT scans in 10 patients showed a median 81% increase in prostate volume 2-5 days after PDT (range, 14-161%). If 1 lobe was treated, up to 49% of the prostate tissue was necrotic, and if both lobes were treated, up to 91% of the CT cross-sectional area was necrotic. In all cases, PSA eventually began to rise again, and 13/14 patients were started on antiandrogen therapy at a median of 10 months (range, 3-38).

Side effects included mild-to-moderate perineal discomfort, irritative urinary symptoms lasting up to 1 month, and acute retention/dribbling. While 6/14 patients' AUA scores normalized by 3 months, 8/14 continued to deteriorate. Four patients developed incontinence, including 2 with occasional leakage and 2 with troublesome stress incontinence. Four of 7 with residual sexual function post-RT suffered irreversible declines in sexual function. Two patients were noted to have superficial rectal ulcers, including 1 who underwent an ill-advised rectal biopsy and subsequently developed a urethrorectal fistula.

Nathan and colleagues concluded that PDT reduced the cancer burden in patients with localized recurrent prostate cancer with a side-effect profile that compared favorably with salvage cryotherapy or surgery. Given improvements in light dosimetry, this minimally invasive procedure is a new option for organ-confined recurrences following failed radiotherapy. If necessary, PDT can be applied 1 or more times to previously irradiated tissue without cumulative toxicity.

COMMENT BY EDWARD J. KAPLAN, MD

Thomas Dougherty at the Roswell Park Cancer Institute in Buffalo, NY, developed photodynamic therapy, which relies on the creation of reactive oxygen species for its cytotoxic effect, 30 years ago. It has been used for a variety of tumors, including bladder, larynx, lung, biliary, naso- and oropharyngeal, and brain cancers.[1] Nathan et al are the first group to publish their experience using an interstitial approach for prostate cancer. In this country, Dr. Eli Glatstein's group at the University of Pennsylvania has been investigating interstitial PDT for prostate cancer using a different photosensitizing agent, motexafin lutetium. So far in the United States, the FDA has approved only porfimer sodium for use. Other photosensitizers being evaluated for use in prostate cancer include tin ethyl etiopurpurin[2] and liposomal benzoporphyrin derivative monoacid ring A.[3]

Tissue penetration is greatest in the red part of the spectrum. Despite this, there can be significant individual variability in light penetration. Lee and associates, in their study of light fluence in 7 prostate cancer patients subjected to PDT, noted that hemorrhage around the light source was a significant, yet unpredictable, impediment to light diffusion into the prostate.[4] Successful PDT is not only dependent upon sufficient light, but also adequate photosensitizer levels and good tissue oxygenation. Tumor hypoxia can hamper the effectiveness of PDT, while hyperbaric oxygen during PDT has been shown to improve PDT results in murine

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mammary tumor models.[5]

It seemed surprising to me that there had never been a clinical report on PDT for prostate cancer, since I have known about PDT since the days of my Masters degree studies at Roswell Park in the early 1980s. This study was actually brought to my attention by several patients. After reading the paper, I can understand my patients' enthusiasm, but unfortunately the reality is that light dosimetry, including fractionation issues and interpatient variability in light diffusion, remains a challenge. Clearly, advancement of this technology for clinical use depends upon overcoming the same sorts of issues that have kept cryotherapy and radiofrequency microwave heating from gaining widespread popularity. ■

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Management of Invasive Carcinoma of the Uterine Cervix Associated with Pregnancy: Outcome in Intentional Delay in Treatment

ABSTRACT & COMMENTARY

Synopsis: *Delay in treatment to allow for fetal maturity is safe in patients with early stage I cervical carcinoma associated with pregnancy.*

Source: Takushi M, et al. *Gynecol Oncol*. 2002;87: 185-189.

Takushi and colleagues retrospectively reviewed the medical records of 28 patients with invasive cervical cancer diagnosed during pregnancy or within 1 month after pregnancy to investigate maternal and neonatal outcomes after planned treatment delay to improve fetal maturity. Twenty-two patients (79%) had stage I disease, and 6 (21%) had stage II or III disease. All but one patient had squamous cell histology. Twenty cases were diagnosed before 22 weeks gestation, 4 between 22 and 36 weeks, 1 after 36 weeks, and 3 were diagnosed postpartum. In the immediate treatment group (n = 16), the stage was IA in 3 cases, IB in 7, and II or III in 6 patients. In 11 patients, hysterectomy was performed after therapeutic abortion or with fetus in situ. In 2 patients, cesarean section was followed by hysterectomy or radiotherapy. Three patients diagnosed postpartum were treated with either hysterectomy or radiotherapy. Fifteen patients were free of disease during the follow-up of 27 to 114 months. In the delayed treatment group (n = 12), the stage was IA1 in 8 cases, IA2 in 1, IB1 in 2, and IB2 in 1 case. In the 8 patients with stage IA1 tumor, the treatment was deferred until term with a delay of 6 to 25 weeks, and hysterectomy or therapeutic conization was performed after delivery. In the 4 patients with stage IA2, IB1, or IB2 tumor, the treatment was postponed until after 30 weeks' gestation with a delay of 6 to 15 weeks. No disease progression was documented. Cesarean delivery was followed by hysterectomy in these patients. All patients were free of disease during the follow-up of 70 to 156 months, and their offspring were well with no sequelae. The authors concluded that delay in treatment to allow for fetal maturity is safe in patients with early stage I cervical carcinoma associated with pregnancy.

■ COMMENT BY DAVID M. GERSHENSON, MD

The association of cervical cancer with pregnancy is fortunately quite rare, occurring in about 1 in 2000 to 10,000 pregnancies. When it does occur, obvious important considerations include the health of the mother and the viability and health of the fetus. No study has demonstrated an adverse effect of pregnancy on the biology or disease progression of the cervical cancer. Of course, there are no large prospective studies on this topic, and there never will be. Historically, cervical cancer in pregnancy was generally treated immediately, with the pregnancy being terminated. With advances in neonatal medicine and improved outcomes for increasingly premature infants, reports of planned delay of treatment began to emerge. This study from Japan certainly confirms the experience from several other studies, most of which originate from the United States. Takushi et al cite 10 other studies in which a small number of patients, 1 to 8, with cervical cancer in pregnancy (stages IA2 to IB2) are managed with delays in treatment of 1 to 32 weeks. And, with rare exception, the outcomes have been favorable.

However, one wonders whether there has been lack of reporting in cases with poor outcomes. For patients with preinvasive cervical disease, the rule of thumb would be close monitoring during the pregnancy without intervention. The same has generally been true of stage IA1 disease (usually confirmed by conization). For those with stage IA2 or more advanced disease, however, firm guidelines become obscured. While the outcomes reported in all these studies are impressive and provide some reassurance that definitive treatment can be safely delayed in some pregnant patients with cervical cancer, this approach must be individualized, and the patient and her family must make the final determination after comprehensive informed consent. One must emphasize, as Takushi et al do, that there are no absolutes here. The precise risk of disease progression associated with treatment delay cannot be ascertained. Underestimation of the extent of disease remains a major concern. In general, for patients with stage II, III, or IV disease, immediate treatment, as practiced in this study, is recommended. The real dilemmas are in those patients with stage IA2, IB1, and IB2 disease. ■

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

Rituximab for Relapsed Lymphoma after Autologous Transplant

ABSTRACT & COMMENTARY

Synopsis: *In a retrospective review of treatment of patients with aggressive lymphoma who had relapsed after stem cell transplantation, single-agent rituximab was shown to induce complete or partial responses in close to 50% of patients. This compares favorably to salvage chemotherapy as reported in prior series.*

Source: Pan D, et al. *Cancer J*. 2002;8:371-376.

For patients with large B-cell or mantle-cell lymphoma, survival after relapse from stem cell transplantation is poor. Pan and colleagues at Memorial Sloan-Kettering Cancer Center performed a retrospective analysis to evaluate single-agent rituximab as treatment under such circumstances. Over an approximate 3-year period, 17 patients with aggressive non-Hodgkin's lymphoma (13 with large B-cell and 4 with mantle cell) were treated with rituximab at 375/m^2 weekly for 4 consecutive weeks. Transplantation had occurred a median of 10 months (range, 2-40 months) before relapse and rituximab therapy. The number of prior therapies, including the autologous stem cell transplantation, was 3 (range, 2-6).

Nine of the 17 patients responded (53%) to rituximab, with 4 complete responses and 5 partial responses. The median progression-free survival for all responders was 13 months (range, 6-18 months). Overall, the rituximab was well tolerated, with no patients developing cytopenias requiring transfusion and only 2 patients experiencing mild infusion-related symptoms.

COMMENT BY WILLIAM B. ERSHLER, MD

This retrospective review included patients treated from 1997 through early 2000. The findings are interesting and certainly support the impression that most oncologists already hold, which is that rituximab is active not only in follicular, well-differentiated lymphoma (for which it currently holds an FDA-approved indication), but as treatment for large-cell lymphoma as well. In fact, rituximab added to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was shown to be superior to CHOP alone when used as first-line therapy for elderly patients with aggressive non Hodgkin's lymphoma (NHL).[1] In patients with mantle-cell lymphoma, rituximab plus Hyper-CVAD resulted in a 2-year failure-free survival of 72%, results that may be comparable to stem cell transplantation.[2] Thus, currently, few patients will reach a point of relapse from stem cell transplantation without prior experience with rituximab.

Nonetheless, the demonstration of single-agent activity of rituximab in chemotherapy-refractory, aggressive lymphoma is of importance. Future investigation might find that schedules that include rituximab following transplant may have fewer or delayed recurrence. Furthermore, there are now radiolabeled anti-CD-20 antibodies, which have yet to be of demonstrable benefit in the treatment of aggressive lymphoma,[3] and it would seem likely that these agents will also be of value in aggressive lymphoma, as adjuncts to chemotherapy or in remission maintenance. ■

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Fixed-Dose Single-Administration Pegfilgrastim vs Daily Filgrastim in Patients Receiving Myelosuppressive Chemotherapy

ABSTRACT & COMMENTARY

Synopsis: *A single fixed dose of pegfilgrastim administered once per cycle of chemotherapy was comparable to multiple daily injections of filgrastim in safely providing neutrophil support during myelosuppressive chemotherapy. Pegfilgrastim may have use in other clinical settings of neutropenia.*

Source: Green MD, et al. *Ann Oncol*. 2003;14:29-35.

The prevention of neutropenia and its infectious sequelae is a clinically important goal in the supportive care of patients receiving chemotherapy. The duration of grade 4 neutropenia and the depth of the nadir correlate with the development of infectious complications.[1,2] Filgrastrim (r-metHuG-CSF) stimulates the production of neutrophil precursors, enhances mature neutrophil function, and decreases neutropenia and its complications. It has become a mainstay of current practice. The filgrastim molecule is cleared by renal and neutrophil-mediated mechanisms with a plasma half-life of 3-4 hours. This necessitates daily administration that often requires patients to travel daily to their physicians. There has been a hardship for some patients, particularly the elderly. Proteins can be modified to significantly increase their half-life by the chemical addition of polyethylene glycol (PEG). This PEG-modification of filgrastim results in a new molecule called pegfilgrastim, which in both experimental animals and healthy human volunteers has decreased renal clearance and increased plasma half-life compared with filgrastim, thus sustaining the duration of the pharmacological effect.[3] Median plasma half-life values of pegfilgrastim are independent of dose, and range from 46 to 62 h. This has potential therapeutic benefit in eliminating the need for daily injections. The present study evaluates a single fixed dose of pegfilgrastim vs the standard daily filgrastim.[4]

COMMENT BY STUART M. LICHTMAN, MD, FACP

Pegfilgrastim has been previously evaluated in a number of clinical trials.[5,6] The trials demonstrated that pegfilgrastim is equivalent to filgrastrim in both efficacy and toxicity. In this study, women with breast cancer receiving doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks for 4 cycles were evaluated.[5] This regimen is associated with an average duration of grade IV neutropenia of 4 days, in the absence of growth factors. Patients were randomized to receive a single subcutaneous dose of pegfilgrastim 6 mg 24 h after chemotherapy administration and repeated with each cycle vs daily filgrastim injections at 5 µg/kg per day. This same design was also used in another phase III trial published by Holmes and colleagues.[6] The major difference in the design of the 2 trials was that the Holmes study used a per weight dosing of pegfilgrastim at 100 µg/kg, while the current trial used the fixed dose of 6 mg. This dose was computed from the phase II data in which comparisons with filgrastim showed similar rates of neutrophil recovery. The primary end point of the current trial, the mean duration of grade IV neutropenia, was 1.8 days for the pegfilgrastim group, and 1.6 days for the filgrastim group in the first cycle.[7] These differences were not significant by the criteria of the trial. The duration of grade IV neutropenia in later cycles of treatment was again comparable between the pegfilgrastim group and filgrastim group. Importantly, no difference was seen in the duration of grade IV neutropenia across the weight quartiles comparing the fixed dose of pegfilgrastim to the per weight dosed filgrastim patients. In addition, adverse events between the 2 groups were similar with bone pain as the predominant adverse event. Examination by weight quartile showed no variation by weight in the reporting of bone pain. There was a decrease in febrile neutropenia in the pegfilgrastim group but this did not reach statistical significance.

The current study confirms the findings of the Holmes trial and extends the equivalence of pegfilgrastim from a per weight dosing to a fixed-dose schedule.[6] In the United States, the indication for pegfilgrastim is "to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia."

Clinical trials are needed to further define the role of pegfilgrastim.[7] This can be with other chemotherapy regimens and in other settings, such as dose-dense regimens of every 2 weeks or even weekly chemotherapy particularly in breast cancer and lymphoma. Other areas of potential study are the alteration in schedule (ie, administering pegfilgrastim on the day of chemotherapy, post-transplant, acute leukemia, and neutropenia not associated with malignancy).

The conclusions were that a single fixed-dose of peg-

filgrastim administered once per cycle of chemotherapy was comparable to multiple daily injections of filgrastim in safely providing neutrophil support during myelosuppressive chemotherapy. Pegfilgrastim may have use in other clinical settings of neutropenia. ■

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Gemcitabine Activity in Nasopoharyngeal Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Type 2 nasopharyngeal carcinoma occurs most commonly in the Far East. However, patients with this tumor are being increasingly treated in North America with the increase in the number of Asian communities, particularly in urban areas. In this trial, patients with recurrent, locally advanced, or metastatic nasopharyngeal cancer who presented to a single institution for a 22-month period were treated with either gemcitabine alone or in combination with cisplatin. The experience indicates that these drugs can safely offer effective palliation. However, the experience presented should be considered exploratory, and larger, randomized studies are still needed to determine the most effective agents, combinations, and clinical circumstances in which such patients should be treated with chemotherapy.*

Source: Ma BB, et al. *Cancer*. 2002;95:2516-2523.

Nasopharyngeal cancer (NPC) is common in Asia, and clinical trials there have indicated that gemcitabine, either alone or in combination with cisplatin, has antitumor activity. North American oncologists are also confronted with increasing numbers of patients with NPC, especially among the increasing numbers of Asian immigrants. In the current report, Ma and colleagues at the Princess Margaret Hospital detail their experience with gemcitabine with or without cisplatin, in patients with NPC. For an approximate 2-year period, 32 patients with NPC were treated with gemcitabine (n = 18) or gemcitabine with cisplatin (n = 14). Patients either received 1000 mg/m^2 gemcitabine (GEM) on days 1, 8, and 15 every 28 days as a single agent, or with cisplatin (GC) given on day 2, at 70 mg/m^2.

Most of the patients (91%) were of Southeast Asian ancestry, and the great majority (91%) had type 2 (World Health Organization 1991 classification) non- keratinizing histology.[1] At the initiation of treatment, 61% of the patients treated with GEM alone and 43% in the GC group had distant metastases. Performance status was also lower for patients receiving GEM alone and prior chemotherapy experience was greater. Before being offered either GEM or GC, patients with local disease recurrence were assessed for eligibility for salvage surgery (radical neck dissection), re-irradiation, or brachytherapy. Thus, included patients were those not eligible to receive further local therapy due to significant risks of damage to normal tissues.

Patients in both groups (GEM and GC) received a median of 4 cycles of chemotherapy. Reduction of the dose of GEM occurred in 17 of 75 cycles (23%) and 18 of 67 cycles (27%) of GC, and the majority of these were due to myelosuppression on day 15, necessitating dose reduction or delays. However, such delays beyond 7 days were reported as "infrequent."

This was not a randomized trial and the GEM group was mostly pretreated (89% had prior chemotherapy). Partial responses were observed in 5 (28%) and 1 patient had a complete response. In the GC group, there were 2 CRs (14%) and 7 PRs (50%), giving an overall response rate of 64%. The median duration of response for the GEM and GC patines was 17 and 24 weeks, and the 1-year survival rate was 48% and 69% respectively. Thus, this report confirms that GEM is an active and tolerable drug for patients with NPC.

■ COMMENT BY WILLIAM B. ERSHLER, MD

North American ENT surgeons and oncologists, particularly those in urban areas, are treating an increased number of nasopharyngeal carcinomas, due in a major way, to the increased numbers of first- and second-generation Asian emigrants.[2] Nasopharyngeal carcinoma had been uncommon in North America, but is endemic in Southeast Asia, North Africa, and the Mediterranean. In these endemic areas, the carcinomas are typically non keratinizing or undifferentiated and are associated with Epstein Barr virus infection. Second-generation, North American-born Chinese emigrants also have a high incidence of this malignancy, estimated to be 6 times greater than Caucasians.[3]

The main objective of this study was to document the

tumor response and toxicity of gemcitabine, with or without cisplatin in patients with nasopharyngeal carcinoma. Previously, reports out of Asia demonstrated the potential use of gemcitabine in patients with recurrent or refractory nasopharyngeal cancer.[4] This report, from the Princess Margaret Hospital in Toronto, affirms this activity and substantiates the role of gemcitabine for palliative treatment of nasopharyngeal carcinoma. Furthermore, the experience indicates that the gemcitabine-cisplatin combination was well tolerated and also effective. However, because the 2 groups were not randomized or comparable with regard to stage of disease and patient performance status, it is impossible to tell from the data presented whether the combination is more effective than either agent alone. Nonetheless, extrapolating from experience with other tumor types, including non-small-cell lung cancer and transitional-cell bladder cancer, the combination is likely to be superior to either single agent alone, and with nonoverlapping toxicities, the 2 drugs can be administered safely.

It should be recalled that the synergism witnessed for gemcitabine and cisplatin is schedule dependent, as the experience with non-small-cell lung cancer has indicated that cisplatin administered on day 2 (at doses of 70 or 100 mg/m^2) was superior to when given on day 1, without affecting hematological toxicity.[5] Therefore, this combination and schedule is a reasonable approach for patients with locally advanced, recurrent or metastatic nasopharyngeal carcinoma. However, before such becomes the standard of care, additional, larger-scale studies are needed. Furthermore, because there were so few patients in the current trial with type 1, keratinizing or differentiated NPC, the application of these findings to patients (more typically Caucasian) would be inappropriate. ■

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4. Which of the following statements about the use of gemcitabine for patients with metastatic or recurrent undifferentiated nasopharyngeal carcinoma is true?

a. Complete remissions are common and overall survival has been prolonged in treated patients.
b. Partial remissions are common, and toxicity has been manageable in treated patients.
c. Partial remissions are common, but observed toxicity (particularly myelotoxicity) limits its utility.
d. Response rates are low and toxicity precludes its common use in this setting.

5. In a retrospective series from Memorial Sloan-Kettering, rituximab has been shown to have single agent activity, producing a complete or partial responses in approximately what percentage of patients?

a. 5
b. 25
c 50
d 75

6. Which of the following is not a requirement for effective interstitial PDT delivery?

a. Good tissue oxygenation
b. Good tissue necrosis levels
c. Good photosensitizer absorption
d. Good light penetration

7. Regarding the Nathan PDT paper, which statement is correct?

a. Patients who received at least 20 J PDT showed excellent PSA responses.
b. All patients received treatment to both prostate lobes.
c. Patients treated with a higher number of laser fibers did better.
d. None of the above.

Answers: 4:b; 5:c; 6:b; 7:d

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In Future Issues:

Radiation Therapy Techniques

PHARMACOLOGY WATCH

FDA Issues 'Black Box' Warning Based on WHI Study

The FDA has mandated a "Black Box" warning for all estrogen and estrogen/progestin products for use by postmenopausal women. The new warnings are based on analysis of data from the Women's Health Initiative (WHI) study that was published July 2002. The box warning emphasizes that these drugs have been associated with increased risks for heart disease, heart attacks, strokes, and breast cancer and that they are not approved for heart disease prevention. Wyeth Pharmaceuticals, the manufacturer of Premarin, Prempro, and Premphase, products that were used in the WHI study, are also required to change their indications to: treatment of severe vasomotor symptoms, vulvar and vaginal atrophy associated with menopause, prevention of postmenopausal osteoporosis, and should only be used when the benefit clearly outweighs the risk. The labeling will also be required to include consideration of other therapies for the atrophy and osteoporosis indications, and to recommend use of the lowest dose for the shortest duration possible. While Wyeth's products are the focus of this initial press release and FDA action, all estrogen products will be subject to new labeling. The FDA is also recommending future research to answer questions regarding the risks of lower-dose estrogen products and if other types of estrogens and progestins are associated with lower risk of CVD and breast cancer. The complete press release can be viewed at www.fda.gov.

ALLHAT: Thiazide for Hypertension Treatment

Thiazide diuretics should be considered first-line therapy for hypertension, according to the authors of the ALLHAT study published in December. In a finding that surprised nearly everyone (especially the sponsors of the study) in patients with hypertension and at least one other cardiovascular risk factor, the diuretic chlorthalidone was associated with better cardiovascular outcomes at less cost and with equal tolerability compared to a calcium channel blocker or an ACE inhibitor. ALLHAT enrolled more than 33,000 patients from 623 centers in the United States, Canada, and the US Virgin Islands. Patients were randomized to the calcium channel blocker amlodipine, the angiotensin-converting enzyme inhibitor lisinopril, or chlorthalidone. Mean follow-up was 4.9 years with the primary outcome being combined fatal CHD or nonfatal MI. Secondary outcomes included all-cause mortality, stroke, combined CHD, and combined cardiovascular disease (CVD). The 6-year rate of the primary outcome and all-cause mortality was virtually identical for all 3 drugs. Chlorthalidone was superior to amlodipine in preventing heart failure (10.2% vs 7.7%, RR, 1.38, 95% CI, 1.25-1.52) and was superior to lisinopril for lowering blood pressure and in 6-year rates of combined cardiovascular disease including stroke (6.3% vs 5.6%) and heart failure (8.7% vs 7.7%). With improved cardiovas-

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cular outcomes, lower cost, and equal tolerability, the study concludes that thiazide-type diuretics are superior in preventing one or more forms of CVD and that they should be the preferred agent in antihypertensive therapy, and should be included in all multidrug regimens (*JAMA*. 2002;288:2981-2997). An accompanying editorial calls ALLHAT "one of the most important trials of antihypertensive therapy" and suggests that national guidelines should be changed to emphasize use of thiazide diuretics as initial therapy (*JAMA*. 2002;288:3039-3042).

Candesartan Effective Against Migraines

The angiotensin II receptor blocker candesartan is effective in preventing migraine headaches, according to a new study. Norwegian researchers looked at 60 patients age 18-65 with 2-6 migraines per month. Patients were randomized in a double-blind placebo-controlled crossover study with the main outcome being number of days with headache. Secondary outcomes included use of pain medications and triptans, hours with headache, headache severity, and days lost from work. During the 12-week study, the mean number of days with headache was 18.5 with placebo vs 13.6 with candesartan (P = .001) in the intention to treat analysis (n = 57). Patients were considered a candesartan responder if they noted a reduction of 50% or more of days with headache (18 of 57 patients, 31.6%) or days with migraine (23 of 57 patients, 40.4%). Although this represented a minority of patients, those who did respond benefited from effective migraine prophylaxis. Candesartan's tolerability profile was comparable with placebo (*JAMA*. 2003;289:65-69).

Cough! No Cold Relief from Echinacea

Echinacea offers no benefit in treating the common cold according to a study from the University of Wisconsin. A total of 148 college students with recent onset colds were randomized to an encapsulated mixture of unrefined Echinacea (*E purpurea* herb and root and *E angustifolia* root) 6 times a day on the first day of illness and 3 times a day on the subsequent days up to a total of 10 days. The main outcome was the severity and duration of self-reported symptoms of URI. No statistically significant differences were detected between Echinacea and placebo groups for any of the measured outcomes, which included trajectories of severity over time or mean cold duration. No significant side effects were noted with Echinacea. The study concludes that no detectable benefit or harm could be found with Echinacea treatment for the common cold (*Ann Intern Med*. 2002;137:939-946).

COX-2 Inhibitors and GI Benefits Could Be Overrated

Could the GI benefits of COX-2 inhibitors be overrated? A new study suggests that the COX-2 inhibitor celecoxib is no safer than a combination of diclofenac plus omeprazole with regard to ulcer risk in patients with a history of peptic ulcer disease and arthritis. Researchers from Hong Kong recruited patients with arthritis and NSAID-related bleeding ulcers. After their ulcers had healed, 287 patients who were negative for *Helicobacter pylori*, were randomly assigned to receive celecoxib 200 mg twice a day plus placebo, or diclofenac 75 mg twice a day plus 20 mg of omeprazole for 6 months. Recurrent bleeding ulcer occurred in 7 patients receiving celecoxib and 9 receiving diclofenac/omeprazole (4.9% vs 6.4%). Renal adverse events including hypertension, peripheral edema, and renal failure occurred in 24.3% of patients receiving celecoxib and 30.8% of those receiving diclofenac/omeprazole. The authors suggest that neither regimen offered effective protection against recurrent ulcer complications or renal adverse effects (*N Engl J Med*. 2002;347:2104- 2110).

FDA Actions

Pfizer's new anti-migraine drug, eletriptan (Relpax) has been approved by the FDA for marketing. The drug that is available in 20-mg and 40-mg tablets has been shown to be effective in aborting migraine headaches within 2 hours. The company is marketing a 80-mg tablet in Europe, but the FDA refused to approve the higher dose due to an increase in adverse events.

Montelukast (Singulair), Merck's leukotriene inhibitor, has been approved by the FDA for the treatment of seasonal allergic rhinitis. The drug has been on the market since 1998 for the treatment of asthma in adults and children. This new indication is the first for a leukotriene inhibitor, and creates a new, nonantihistamine treatment modality for this indication. Montelukast was approved for symptoms of seasonal allergic rhinitis in adults and children aged 2 years and older. It is available in 10 mg strength for adults, and a chewable 4 mg or 5 mg strength for children. ■