

# Bone Pain Flags Worse Survival in Prostate Cancer

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CHICAGO — Once bone pain appears in patients with hormone-refractory prostate cancer, it is often too late for docetaxel therapy to have an impact on their survival, according to a poster presentation at the annual meeting of the American Society of Clinical Oncology.

For this reason, docetaxel (Taxotere) should be started earlier, when it can do

some good, said Dr. Stéphane Oudard, professor of medicine at Georges Pompidou European Hospital, Paris.

He and his colleagues conducted a retrospective analysis of 145 consecutive chemotherapy-naïve, hormone-refractory prostate cancer patients. The median 3-year survival rate for 25 patients with moderate or severe pain within the 90 days of starting chemotherapy was 4% vs. 11% for 41 patients who had mild pain, and 29% for the 79 patients who had no or minimal pain. One-year survival was 52%, 56%, and 75%, respectively.

Patients with minimal or no pain survived a median of 21.4 months; those with mild bone pain 15 months, and

those with moderate or severe pain 13.1 months.

Bone pain in hormone-resistant prostate cancer patients is usually associated with poor Eastern Cooperative Oncology Group (ECOG) performance status, short prostate-specific antigen (PSA) doubling time, more aggressive disease, and worse prognosis. The study was designed to explore the impact of the presence and intensity of bone pain on overall survival, and also to test the link between PSA doubling time and survival of patients with minimal or no pain.

To do so, the researchers retrospectively analyzed their institution's database of 145 consecutive chemotherapy-

naïve patients who had failed androgen blockade and anti-androgen withdrawal. Patients had an ECOG performance status of 2 or less and were treated with docetaxel 70-75 mg/m<sup>2</sup> or mitoxantrone (Novantrone) 12 mg/m<sup>2</sup> every 3 weeks and prednisone 10 mg/day, continuously. The mean age of the patients was 68 years, 93% (135 patients) had bone metastases, and 55% had minimal or no pain at baseline. Median survival reached 32.4 months in those who had minimal or no pain at baseline and whose PSA doubling time was equal to or more than 45 days. It was 16.5 months in those with comparable pain at baseline and a PSA doubling time of 45 days or less. ■

## LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia<sup>2</sup> (2% and <1%). \*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo B Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). §Denominator used was for females only (N=490 Lexapro; N=404 placebo). ¶Generalized Anxiety Disorder Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder\* (Lexapro (N=429) and Placebo (N=427)).

**Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating/Increased (4% and 1%); Central & Peripheral Nervous System Disorders: Headache (24% and 17%); Parosmia (2% and 1%); Gastrointestinal Disorders: Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%); Musculoskeletal: Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder<sup>1,2</sup> (14% and 2%); Anorgasmia<sup>2</sup> (6% and <1%); Menstrual Disorder (2% and 1%). \*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo B Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). §Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events:** The potential dose dependency of common adverse events (defined as an incidence rate of 15% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. TABLE 4. Incidence of Common Adverse Events\* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125); Insomnia (4%, 7%, 14%); Diarrhea (5%, 6%, 14%); Dry Mouth (3%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating/Increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 6%); Indigestion (1%, 2%, 6%). \*Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs:** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 5 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=407) and Placebo (N=383); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=737) and Placebo (N=636)); Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Praprim has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes:** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes:** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes:** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes:** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo, and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro:** Following is a list of adverse events that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. Cardiovascular - Frequent: palpitation, hypertension. Infrequent: bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - Frequent: light-headed feeling, migraine. Infrequent: tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - Frequent: heartburn, abdominal cramp, gastroenteritis. Infrequent: gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - Frequent: allergy, pain in limb, fever, hot flushes, chest pain. Infrequent: edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - Infrequent: bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - Frequent: increased weight. Infrequent: decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - Frequent: arthralgia, myalgia. Infrequent: jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - Frequent: appetite increased, lethargy, irritability, concentration impaired. Infrequent: jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness, nervous, crying, abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female - Frequent: menstrual cramps, menstrual disorder. Infrequent: menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. \*Based on female subjects only. †N=305 Respiratory System Disorders - Frequent: bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. Infrequent: asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - Frequent: rash. Infrequent: pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - Frequent: vision blurred, linitus. Infrequent: taste alteration, sarcoche, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - Frequent: urinary frequency, urinary tract infection. Infrequent: urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram:** Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leukopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

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## Stress Coaching Eases Radical Prostatectomy Fears

CHICAGO — Just 2 hours of teaching men with prostate cancer how to self-manage their stress improves their ability to cope with their fears of undergoing radical prostatectomy.

Moreover, the effects of learning how to manage their stress are long-lasting, and could ultimately result in less cost to the health care system, according to a poster presented at the annual meeting of the American Society of Clinical Oncology.

Researchers at the University of Texas M.D. Anderson Cancer Center and Baylor College of Medicine, both in Houston, randomized 150 men with early-stage prostate cancer attending their urology clinics to receive stress management, supportive attention, or usual care.

Stress management consisted of two individual sessions, each 45-60 minutes long, with a clinical psychologist 2 weeks before surgery. During those sessions, the men were taught relaxation techniques including diaphragmatic breathing and guided imagery. They also received coaching on what would happen on the day of surgery and were given coping skills to use after their surgery. In addition, they had one brief, 5-10-minute session on the morning of their surgery, and another brief session

2 days after surgery. The men were also given a stress management guide and an audiobook to help them practice deep breathing and guided imagery at home.

Supportive attention consisted of two individual sessions, each 45-60 minutes long, with a clinical psychologist 2 weeks before surgery, in which the men discussed their fears but were not taught any relaxation skills. They also had two brief sessions—one on the morning of surgery and one 2 days afterward. The third group received standard medical care, and did not meet with a psychologist.

All of the men completed psychosocial and quality-of-life measures at baseline and 6 and 12 months after surgery. Most men were Caucasian (78%), married (85%), and highly educated (80% with some college or higher education).

After controlling for age, ethnicity, marital status, disease stage, baseline prostate-specific antigen, Gleason score, and baseline test scores, the researchers found that

men who received either stress management or supportive attention had significantly less distress in the week prior to surgery than did the usual-care group.

On the morning of surgery, those who learned to manage their stress had the least distress, followed by those who got supportive attention. Those who received usual care had the greatest distress. "There was a clear dose-response effect [showing] that a very brief, two-session encounter can really buffer some of the distress and anxiety about going into surgery," said Dr. Lorenzo Cohen, Ph.D., chief of the integrative medicine section in the department of palliative care and rehabilitation medicine at M.D. Anderson Cancer Center.

"These patients had less interference in their ability to engage in physical functioning, reported less bodily pain and better general health scores as far out as 12 months later. These results strongly suggest that one needs to incorporate some form of stress management [before surgery]." ■



Patients reported better general health scores as far out as 12 months after the sessions on stress management.

DR. COHEN

## Quality of Life Tops List of Concerns in Prostate Cancer

CHICAGO — The major worry of men with prostate cancer to rank 18 issues on a 5-point scale according to their importance. The survey was conducted anonymously over a 3-day period.

The finding, from a Web-based survey of 2,128 men with prostate cancer, was "surprising, but not shocking" lead researcher, Dr. Richard J. Gralla, president of the New York Lung Cancer Alliance in New York City, said in an interview.

Sex also was a major concern of the men, he noted, much more than pain but less than not being able to sleep.

Dr. Gralla and colleagues collaborated with NexCura, (www.nexcura.com), a patient information resource on the Internet, which mandates that people register to use the site.

The investigators invited men with prostate cancer to rank 18 issues on a 5-point scale according to their importance. The survey was conducted anonymously over a 3-day period.

Following good quality of life, the next four most important concerns were maintaining independence, ability to sleep, sexual functioning, and incontinence.

"Sleep was ranked very highly by the patients. It was a surprise to me to see how important this was," Dr. Gralla said.

Another surprise was the importance of maintaining independence.

"We thought this might be because our survey respondents were all men, and it might be a gender-specific thing to fear becoming dependent. But we have since done the same thing for patients with lung cancer, where half the respondents are

women, and have seen the same result."

Hot flashes, which many physicians think would be important to the men who have them, ranked near the bottom of respondents' concerns. So did pain, and poor appetite. "For families, eating, weight loss, appetite, are all very important, but the patients do not rank these so highly," Dr. Gralla said.

"Using this Web-based program, we were able to get opinions from over 2,000 patients with prostate cancer, which is far and away the largest effort for content validity," he said "Patient-reported outcomes, or PROs, can yield interesting and important information that may be more accurate than health professionals have heretofore expected, and provide a very good way for patients to be able to communicate with health care professionals." ■