[News * Analysis * Commentary * Controversy]

December 10, 2013 * Vol. 35 * No. 23

oncology-times.com

ONCOLOGY TIMES

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Is Breast Conservation Underutilized in Men with Localized Breast Cancer?

BY HEATHER LINDSEY

Gender bias and assumptions about men are being made when they aren't given the option of breast-conserving treatment, said the lead researcher of a large database review that uncovered the findings. In addition, when compared with the situation in women, men with locally advanced disease are less likely to receive postmastectomy radiation. *Page 18*

Hyman Muss on How He Treats Elderly Patients with Breast Cancer p.10

Myeloma:

- Promising Treatment Updates for Patients with Relapsed/Refractory Disease
- Is Maintenance Therapy Needed; and If So, with What? pp.23, 24

Dexamethasone a Potential Treatment for Cancer-Related Fatigue p.31

PERIODICALS

[ALSO]

SHOP TALK 6
Future of Accelerated Partial Breast Irradiation in Question 42
WENDY HARPHAM: Patient Handout: Facing Recurrent Cancer 44
Radioiodine-Refractory Thyroid Cancer Shown as Responsive to Dabrafenib 45
CONFERENCES 46

Dexamethasone a Potential Treatment for Cancer-Related Fatigue

BY HEATHER LINDSEY

Dexamethasone helps to reduce cancer-related fatigue in patients with advanced disease, according to a double-blind, randomized, placebo-controlled trial published in the *Journal of Clinical Oncology* (***2013;31:3076-3082***).

This study will "definitely" impact clinical practice, said lead author Sriram Yennu, MD, Associate Professor in the Department of Palliative Care and Rehabilitation Medicine at the University of Texas MD Anderson Cancer Center.

"Prior research demonstrating the benefit of steroids in advanced cancer patients is limited, and there are no validated studies using fatigue as a primary outcome," he said. The study he led (senior author was Eduardo Bruera, MD) used validated tools in a controlled setting that met National Cancer Institute and National Comprehensive Cancer Network criteria. Moreover, the study demonstrated that dexamethasone at 4 mg twice daily was effective in treating cancer-related fatigue for a period of two weeks.

"It is not uncommon for patients with advanced cancer to receive corticosteroids because of previously published data," commented Tracey O'Connor, MD, Associate Professor in the Department of Medicine at Roswell Park Cancer Institute. Many clinicians have experience, through some trial and error, with steroids in this patient population, and this randomized, placebo-controlled study helps validate current clinical practice, she said. "I hope this research will help generalize the practice a bit more for oncologists who haven't already tried giving the drug."

SRIRAM YENNU, MD: "On the basis of the data from this study, future research should investigate the mechanism of action and the most beneficial and safe type, dosage, and route of steroids for the treatment of cancer-related fatigue in patients with advanced cancer."

Even if this particular study does not affect clinical practice, the time span for further research to have an impact probably won't be that long, said Harold Goforth, MD, of the Solid Tumor Oncology Department at Cleveland Clinic. "We really have poor choices for cancer-related fatigue."

Study Details

The study included 84 patients with advanced cancer—43 taking dexamethasone at 4 mg twice daily and 41 receiving placebo, with a 15-day follow-up. The patients were being treated in outpatient clinics for palliative care, pain management, and oncology at MD Anderson, or were outpatients at either Lyndon B. Johnson General Hospital in Houston or Four Seasons Hospice in Flat Rock, N.C.

The patients had at least three symptoms of cancer-related fatigue—specifically, pain, fatigue, chronic nausea, anorexia/cachexia, sleep problems, depression, or poor appetite, with a score of 4 or more on a scale of 0 to 10 on the Edmonton Symptom Assessment Scale (ESAS).

At day 15, the primary endpoint of the Functional Assessment of Chronic Illness–Fatigue (FACIT-F) subscale was significantly higher in patients receiving dexamethasone than in those taking placebo (9 ± 10.3 vs. 3.1 ± 9.59). FACIT-F total quality-of-life scores were also significantly better at day 15 in the dexamethasone group than in placebo patients (18.16 ± 22.88 vs. 7.87 ± 19.93).

The ESAS physical distress score at day 15 was also significantly better for the dexamethasone group than the placebo group (-10.86 ± 9.55 vs. -4.78 ± 10.86). However, the investigators did not report any significant differences in the ESAS scores of overall symptom distress or psychological distress.

While dexamethasone did not have a significant impact on anxiety or depression outcomes as measured by the Hospital Anxiety and Depression Scale (HADS), the drug did significantly improve Functional Assessment of Cancer Therapy–Anorexia-Cachexia (FAACT) scores at day 15 compared with placebo (6.82 ± 8.95 vs 1.95 ± 8.54).

TRACEY O'CONNOR, MD: "I hope this research will help generalize the practice for oncologists who haven't already tried giving the drug."

The frequency of adverse events was not significantly different between those taking dexamethasone and placebo, the researchers reported.

Why 15-Day Follow-up?

Limiting the study period to 15 days was intentional, Yennu said. Since this patient population is frail symptomatically and has advanced disease with limited life expectancy, providing prompt relief is a priority. Moreover, the dropout rate, which was approximately 28 percent, might have been even higher with a longer follow-up time, he said.

O'Connor pointed out that this is a very difficult population to study because patients generally are symptomatic close to the end of life, and many factors such as disease progression can affect participation. She said that while a longer follow-up would be desirable, the fact that positive effects were demonstrated at day 15 is highly encouraging.

Jennifer Obel, MD, a medical oncologist at NorthShore University HealthSystem in Evanston, III. who specializes in gastrointestinal oncology, said that because many patients are living long-term with advanced cancer, further studies focusing on 30 to 45 days out would be valuable. "We need to understand what side effects associated with dexamethasone will emerge," she said.

Also asked for his opinion, Thomas W. LeBlanc, MD, MA, Assistant Professor of Medicine in the Division of Hematologic Malignancies and Cellular Therapy at Duke University School of Medicine, said that while prior studies suggest that the drug may be effective only for a couple of weeks, "what happens after 30 or 60 days—Do you lose the benefits and just have toxicity, or do the benefits last longer?"

continued on page 32

"Many clinicians have experience, through some trial and error, with steroids in this patient population, and this randomized, placebo-controlled study helps validate current clinical practice."

→CANCER-RELATED FATIGUE

continued from page 31

"Future studies need to determine the subgroups of patients most likely to benefit from dexamethasone and the impact of dexamethasone resistance on CRF [cancer-related fatigue] reduction and the occurrence of adverse effects.

Goforth said he suspects that longer studies of up to 60 days would show that the treatment benefit with dexamethasone decreases over time. "Patients generally rally when steroids are added to their treatment, but as they become adjusted to the medication, the early effects generally wane," he said. "This is true for appetite and the burst of energy you get."

Dexamethasone for Short-term Goals

Using the evidence provided in the current study, oncologists can prescribe dexamethasone for fatigue and possibly other symptoms such as pain, loss of appetite, shortness of breath, and overall well being in patients with advanced cancer, Yennu said. And while the results weren't statistically significant for all of these symptoms, this may have been due to the dosage used.

JENNIFER OBEL, MD: "We need scientifically rigorous trials focused on methods for improving patients' symptoms, whether through medications like dexamethasone, or psychological interventions."

Oncologists should also keep in mind that "most terminally ill patients want a good quality of life before they die," he said. "They want more energy to spend time with their family."

Short-term improvements in fatigue may be what some patients need to achieve personal goals such as attending a wedding or graduation, Goforth said. "In these situations, you could look at using dexamethasone to perhaps give patients enough energy, drive, and stamina to get to the event."

In patients with more chronic disease, oncologists need to consider both the short- and long-term side effects of the drug, Yennu said.

Side Effects of Dexamethasone

Practitioners should be aware of the side effects associated with dexamethasone, such as water retention and glucose tolerance abnormalities, Goforth said. "It's not a benign drug, so oncologists need to carefully weigh the risks and benefits when determining when to use it for soft indications such as with cancer fatigue."

Thrush and proximal muscle weakness are other potential side effects oncologists need to consider, O'Connor said.

Such adverse events "become more problematic the longer patients are on the medicine," said Robert Taylor, MD, Medical Director of the Center for Palliative Care at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

"Consequently, in patients with a limited life expectancy, such as those in hospice or with less than a month to live, considering dexamethasone is a reasonable option to consider."

To help avoid adverse events, patient selection is important, he noted. For example, in the Yennu et al study, patients with diabetes were excluded, since they may experience complications while on steroids such as, for example, elevated glucose, he said.

LeBlanc said using dexamethasone is "reasonable in select patients—In other words, from what little the literature tells us at this point, I would not recommend prescribing it to all patients with cancer-related fatigue, nor would I recommend long-term use. Clinicians must make a case-by-case assessment of the drug's potential risks and make individualized decisions about whether a short trial of dexamethasone is warranted. We just don't know how long the drug is helpful for."

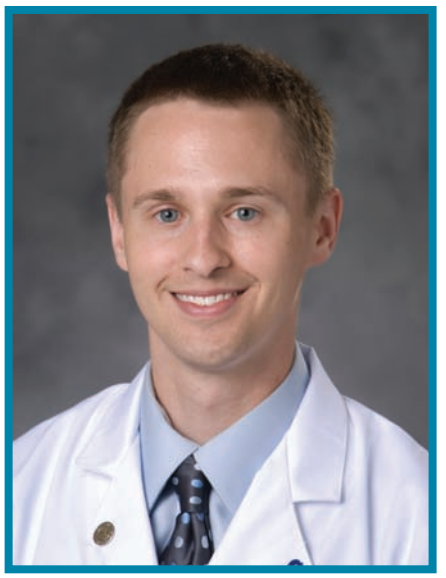
Further Research

Further research needs to include a longer follow-up period and a more robust assessment of the potential side effects of dexamethasone, he continued. "The question is whether oncologists can use these medicines for supportive care earlier in the course of cancer treatment."

Yennu said that in addition to conducting a study with longer follow-up, research evaluating a higher dose of the drug on all dimensions of fatigue would be valuable. Additionally, investigating the effects of dexamethasone on both physical and psychological aspects of fatigue would be interesting.

He said he would also like to investigate adding interventions such as exercise

HAROLD GOFORTH, MD: "Even if this particular study does not affect clinical practice, the time span for further research to have an impact probably won't be that long. We really have poor choices for cancer-related fatigue."



THOMAS LEBLANC, MD: "Using dexamethasone is reasonable in select patients, but I would not recommend prescribing it to all patients with cancer-related fatigue, nor would I recommend long-term use. Clinicians must make a case-by-case assessment of the drug's potential risks and make individualized decisions about whether a short trial of dexamethasone is warranted."

or cognitive behavioral therapy to dexamethasone to see if a more robust response is possible and assess whether the drug has an impact on the psychological and cognitive dimensions of fatigue in addition to the physical dimension.

Taylor agreed: As the study authors noted, more research on dexamethasone's mechanism of action and its suppression of cytokines associated with the symptom cluster of pain, anorexia, weight loss, and fatigue would also be welcome, he said.

Obel said that overall, oncologists need more studies investigating ways to improve cancer symptoms with medications and other interventions that can be easily incorporated into clinical practice. "We need scientifically rigorous trials focused on methods for improving patients' symptoms, whether through medications like dexamethasone, or psychological interventions."