


# OLD DRUGS, NEW POSSIBILITIES

SOON AN ANTIBIOTIC, AN ANTIDEPRESSANT, A SPICE AND A WAKEFULNESS-PROMOTING AGENT MAY BE TESTED IN VARIOUS COMBINATIONS AS TREATMENTS FOR FIVE SPECIFIC CANCER-RELATED SYMPTOMS: FATIGUE, PAIN, SLEEP DISTURBANCE, LACK OF APPETITE AND DROWSINESS.

by Sandi Stromberg

A close-up photograph showing a hand holding a metal spoon, pouring a bright yellow powder into a clear glass jar. The powder is captured mid-pour, creating a dynamic, flowing shape. The background is a solid, dark red color, which makes the yellow powder stand out prominently. The lighting is focused on the powder, highlighting its fine texture and vibrant color.

CURCUMIN, DERIVED FROM CURCUMA LONGA, IS THE MAIN INGREDIENT OF THE COMMON YELLOW SPICE TURMERIC. CURCUMIN HAS PROPERTIES THAT MAKE IT AN EXCELLENT CANDIDATE FOR SYMPTOM CONTROL. IN ANIMAL MODELS, CURCUMIN HAS BEEN SHOWN TO SAFELY SUPPRESS PAIN, DEPRESSION AND EXERCISE-RELATED FUNCTIONAL IMPAIRMENT.

**UNDER THE GUIDANCE OF CHARLES CLEELAND, PH.D. — the ever-diligent detective who has spent his career tracking cancer-related symptoms and assessing clues to unlock their mystery — interventions may be as close as a combination of these four tried-and-true agents.**

While his early investigations centered on pain, in the last few years, he and his colleagues in the Department of Symptom Research have widened their search to include other symptoms. They also have involved other health care professionals across M. D. Anderson: first, to identify symptoms that are general to all cancer patients and, then, to ascertain which are particular to specific types of cancer.

Based on their findings in patients with head and neck cancers and non-small cell lung cancer, they recently received federal funding to plan two randomized clinical trials, which will aim to test combinations of antibiotics and other agents, including curcumin (a component of the spice turmeric) to reduce the severity of cancer treatment-induced symptoms.

“It’s an exciting opportunity,” says Cleeland, chair of the Department of Symptom Research and principal investigator on the renewal of this National Cancer Institute grant. “One of the problems with symptom research to date has been the lack of a strong evidence base. We’ve been working in somewhat of a vacuum. Now we have the funding to get good clinical trial information about a general and very accessible approach to symptoms.”



CHARLES CLEELAND, PH.D., IS THE PRINCIPAL INVESTIGATOR ON A RESEARCH PROGRAM THAT WILL STUDY THE EFFECTS OF COMBINATIONS OF TREATMENTS ON THE SEVERITY OF TREATMENT-RELATED SYMPTOMS IN PATIENTS WITH LUNG AND HEAD AND NECK CANCERS. THE STUDIES, FUNDED BY THE NATIONAL INSTITUTES OF HEALTH, WILL USE COMMON TREATMENT AGENTS AND NOVEL STATISTICAL APPROACHES TO IDENTIFY THE MOST EFFECTIVE TREATMENT COMBINATIONS.

## A CONSTELLATION OF IMPACTS

The clinical trials will continue the work Cleeland and his symptom researchers began several years ago with clinical investigators David I. Rosenthal, M.D., professor and director of Head and Neck Translational Research, and Zhongxing Liao, M.D., associate professor, both in the Department of Radiation Oncology.



Together, they defined the specific symptoms patients with these cancers experience in response to treatment, creating two of the M. D. Anderson symptom inventories, the MDASI-HN (head and neck) and the MDASI-Lung.

“These patients start off with very few or no symptoms at diagnosis,” Cleeland says. “Then, from chemoradiation they develop a constellation of symptoms that we’ve learned are associated with very aggressive cancer therapy. These can cause significant distress and are poorly controlled despite standard supportive care.”

Growing scientific evidence suggests that symptoms occur in clusters and that common biologic mechanisms, such as inflammatory cytokines (signaling proteins), may cause or contribute to these clusters. Cleeland’s group hopes that by investigating various combinations of these drugs with broad anti-inflammatory properties and low toxicity, it will be able to reduce the most severe symptoms caused by these treatments: fatigue, pain, sleep disturbance, lack of appetite and drowsiness (in lung cancer patients) or difficulty swallowing (in head and neck cancer patients).

Not only is this symptom burden unpleasant for patients, but it also can jeopardize their job and, subsequently, their health benefits. Some symptoms may become so severe that patients need a treatment “holiday” or must completely discontinue treatment.



## AREA UNDER THE CURVE

“One of the novel things about this study is that we’re picking five of the most frequent and severe symptoms that we’ve uncovered in our earlier studies and with these agents aiming for what we call an ‘area under the curve,’” Cleeland says.

In the proposed clinical trials, researchers will track the impact that interventions have over a period of time, using an interactive voice response system. A computer will call patients who, using their telephone keypad, will self-report the severity of their symptoms on a scale of 0-10, 0 being “not present” and 10 being “as bad as you can imagine.”

By charting responses, Cleeland and his group will know that treatment is successful if the peak in symptom severity is reduced. For example, if overall fatigue drops from a 5 to a 2 (on the 0-10 scale) over time, this will be reflected in the area under the curve. Comparing the areas under the curve for two treatments will give a clear indication of which treatment better reduces patients’ symptom burden (see figure on page 17). The lower the area under the curve, the more successful the treatment.

“While this is a pretty familiar concept,” Cleeland says, “the unusual thing is that we plan to apply it to symptoms.”



CANCER SURVIVORS KNOW BEST WHAT THE SIDE EFFECTS OF CANCER AND ITS TREATMENTS ARE. YET, THEY OFTEN LACK THE WORDS TO DESCRIBE WHAT THEY FEEL AND THE APPROPRIATE TOOLS FOR SELF-REPORTING. GATHERING SYMPTOM-RELATED DATA TO IMPROVE SURVIVORS’ DAILY LIVES IS THE CENTRAL FOCUS OF M. D. ANDERSON’S DEPARTMENT OF SYMPTOM RESEARCH.

**OLD BECOMES NEW**

Unlike curative cancer treatments, symptom-focused treatments are rarely tested in combination. Now, the two proposed trials will allow Cleeland and his team the unique opportunity to evaluate the effectiveness of combining therapies.

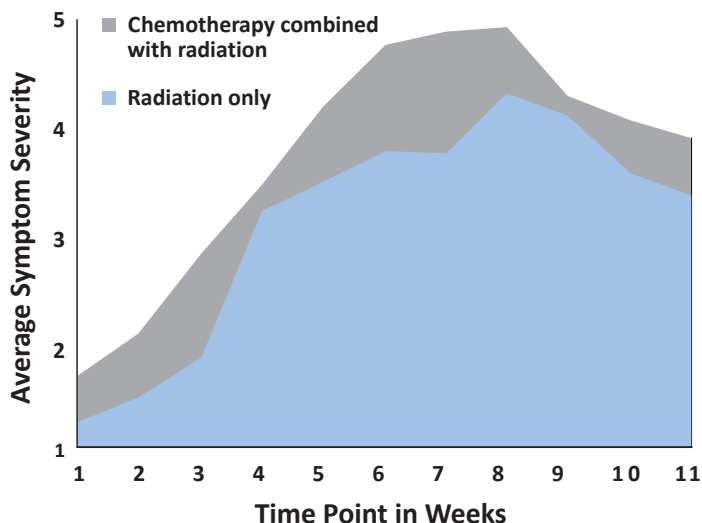
“After a certain point in time, when everything has been tested a little, additional patients will be assigned to the study treatment, depending on how each agent or combination of agents is. It’s somewhat like running a Phase I-II trial,” Cleeland says.

This approach is possible because the trials will use the Bayesian adaptive randomization design instead of the classic randomized clinical trial approach. Valen Johnson, Ph.D., professor and deputy chair of the Department of Biostatistics, developed the design for this novel approach to treatment assessment, the first of its kind to be used in a clinical trial based on patient report of symptom severity.



NYMA SHAH, PROGRAM MANAGER IN THE DEPARTMENT OF SYMPTOM RESEARCH, COLLECTS SYMPTOM INFORMATION DURING A PATIENT INTERVIEW. PATIENTS PROVIDE THE SAME SYMPTOM INFORMATION FROM HOME USING A COMPUTERIZED, TELEPHONE-BASED INTERACTIVE RESPONSE SYSTEM.

**AVERAGE AUC COMPARISON OF 5 SYMPTOMS BY TYPE OF TREATMENT IN PATIENTS WITH HNC**



This area under the curve (AUC) provides a telling visual representation of a comparison of two treatments (chemotherapy combined with radiation versus radiation only) as reflected in the severity of five symptoms (pain, fatigue, sleep disturbance, lack of appetite and difficulty swallowing). Over 11 weeks of treatment, patients receiving radiation therapy alone reported less severe symptoms than the patients receiving the combination therapy, indicated by the smaller AUC.

The Bayesian design allows for smaller, more informative trials. As results about the effectiveness of each agent or agent combination accumulate, they can be incorporated into the study and patients can be assigned to the treatments that are the most effective. Less successful treatments will be dropped. Continual comparing and re-comparing of treatments throughout the course of the trial should eventually whittle the possible combinations of treatments down to only those that are the most effective for reducing symptoms.

In addition, due to the minimal toxicities and interactions that these agents have with one another, the method also makes it possible to assign multiple treatments to the same patients.

“The exciting thing for me is that the more we can do here, the better,” Cleeland says. “It used to be that the side effects of therapies were so horrible you sort of closed your eyes and treated. Doctors at M. D. Anderson have a sense now that symptoms can be treated, and as our co-investigators they want to help patients in a way that leaves them with less symptom burden.”