First-Line Low-Dose Morphine Is Better for the Control of Moderate Cancer Pain Than Weaker Opioids

Using low-dose morphine as a first-line treatment for opioid-naïve patients with moderate cancer-related pain provided improved pain control versus initiating treatment with weaker narcotics, according to the results of a recent study (J Clin Oncol [published online ahead of print December 7, 2015]. doi: 10.1200/JCO.2015.61.0733).

The current guidelines of the World Health Organization (WHO) for cancer-related pain include a 3-step approach using nonopioid analgesics, followed by weak opioids such as codeine or tramadol and then stronger opioids. Although other guidelines, such as those from the National Comprehensive Cancer Network and the European Association for Palliative Care, have recognized that the approach using stronger opioids first is valid, the data behind the recommendations are weak.

“Since conclusive data were lacking as to whether moderate pain should be treated with either step II weak opioids or low-dose step III strong opioids, we studied whether it is possible to abolish the second step in a randomized controlled trial,” says the study’s first author Elena Bandieri, MD, medical oncologist at the Local Health Unit in Modena, Italy, and co-author Mario Luppi, MD, PhD, professor of hematology at the University of Modena and Reggio Emilia Medical Center and Polyclinic, also in Modena.

“Studies such as this are relevant because cancer pain is often inadequately assessed and managed,” says Susan Urba, MD, professor of medicine in the division of hematology/oncology and medical director of the symptom management and supportive care program at the University of Michigan Comprehensive Cancer Center, based in Ann Arbor. “However, awareness of the importance of symptom management has increased. Physicians need to address the topic of cancer pain at every clinic visit.”

Study Details
Researchers across 17 oncology centers in Italy recruited 240 opioid-naïve patients with cancer who were experiencing moderate cancer-related pain. Moderate pain was defined as a score of 4 to 6 on the numerical rating scale (range, 1-10). The patients were randomized to receive either low-dose oral morphine or a weaker opioid for the trial duration of 28 days. The group on the weak opioid treatment arm received oral tramadol alone or in combination with paracetamol (acetaminophen), or codeine in fixed combination with paracetamol. The dose was titrated up, if necessary, to the maximum recommended dose: 240 mg/day or 180 mg/day in fixed combination with paracetamol for codeine and 400 mg/day or 300 mg/day for tramadol if patients were aged older than 75 years. The maximum daily dose of paracetamol was set at 4000 mg/day. Patients randomized to morphine underwent a 3-day titration phase with normal-
release oral morphine up to 30 mg/day, followed by continued treatment with slow-release morphine.

The groups were well balanced with regard to characteristics such as overall symptom severity, type and intensity of pain, Karnofsky performance status, and current antitumor treatment. Of note, approximately 50% of patients in the group receiving the weak opioid and approximately 60% of patients in the group receiving the strong opioid were undergoing antitumor therapy. “Enrolling patients from the oncology and hematology wards, rather than only terminally ill patients, either in hospices or followed by palliative care services, is a strength of our study,” say Drs. Bandieri and Luppi. They note this makes the results relevant for a multitude of practitioners: those providing end-of-life care as well as those providing active cancer therapy.

**Key Findings**

Approximately 88% of patients in the morphine group achieved a response, defined as at least a 20% reduction in pain intensity on the numerical rating scale. In comparison, 55% of patients in the group treated with the weak opioid achieved a response ($P < .001$). Those in the morphine group were also more likely than those in the group receiving the weak opioid to have a highly meaningful response, defined as at least a 50% reduction in pain (76% vs 42%, respectively, $P < .001$).

Other outcomes demonstrating more effective management with morphine include the finding that 35% of the patients in the group receiving the weak opioid had to switch to a strong opioid and 16% of patients in the group receiving morphine switched to a different strong opioid ($P = .001$), whereas 61% of patients in the morphine group and 40% of those patients receiving the weak opioid required no dosage adjustment or drug change over the study period ($P < .002$). In addition, the general condition of patients, which was based on the Edmonton Symptom Assessment System score, was significantly better in the morphine group than in the group of patients receiving the weak opioid at the end of the study period. The Edmonton Symptom Assessment System addresses the overall condition of the patient by rating symptoms such as pain, tiredness, nausea, depression, anxiety, drowsiness, lack of appetite, feelings of well-being, and shortness of breath.

The study found no significant differences between the 2 groups with regard to the frequency or severity of opioid-related adverse events, such as constipation or dizziness.

**Practice Implications**

“The main point is that clinicians do not always have to start on the lowest level of the World Health Organization analgesic ladder for a patient who has moderate cancer pain, even if that patient is opioid-naive,” says Dr. Urba. “The initiation of a low dose of the strong opioid morphine allowed a higher percentage of patients to have earlier and more significant pain relief, compared to those treated with a weak opioid.”

One potential drawback of the study is its open-label design. “It would have minimized bias if the study was blinded so that the patient and physician didn’t know which treatment arm the patient had been randomized to. Also, in the United States, one of the most commonly used weak opioids is hydrocodone, but that analgesic was not included in this trial,” says Dr. Urba.

The authors agreed that a potential weakness of the study is its open-label design. However, it did allow clinicians to titrate the morphine to the optimal dose on a personalized basis, and also to rotate to the alternative opioid rapidly in the event of uncontrolled pain and/or side effects. “This study lends support to abolishing step II of WHO guidelines in many patients, which should be confirmed by further phase 3b/4 trials. This will simplify treatments and perhaps give cancer patients better pain control,” say Drs. Bandieri and Luppi.

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