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Safety and Efficacy of Once-Daily Hydromorphone Extended-Release Versus Twice-Daily Oxycodone Hydrochloride Controlled-Release in Chinese Patients With Cancer Pain: A Phase 3, Randomized, Double-Blind, Multicenter Study

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Abstract: **Noninferiority of the efficacy of once-daily hydromorphone hydrochloride extended-release (hydromorphone ER) compared with twice-daily oxycodone hydrochloride controlled-release (oxycodone CR) was investigated in this randomized, double-blind study in Chinese patients with moderate to severe cancer pain requiring strong oral opioid analgesics. Randomization (1:1) to hydromorphone ER (8–32 mg) or oxycodone CR (10–40 mg) was followed by dose titration (up to 8 days) and dose maintenance (28 days, weekly visits). Primary endpoint was change from baseline to end of study in "worst pain in the past 24 hours" of Brief Pain Inventory (Short Form) score on last observation carried forward (per protocol set). A total of 137 of 260 randomized patients completed maintenance phase (hydromorphone ER: n = 70; oxycodone CR: n = 67); per protocol set: 81 patients. Mean age was 53.1 years (range: 18–70 years; males: 65.3%); most common Eastern Cooperative Oncology Group performance status = 2. Least square mean difference between 2 treatment groups for primary endpoint using analysis of covariance (baseline score, covariate) was −.1 (95% confidence interval: −1.3, 1.1), with upper bound of 95% confidence interval <1.5 (predefined noninferiority margin). Most common reason for deaths was disease progression (hydromorphone ER: 6.3%; oxycodone CR: 12.7%). Treatment-emergent adverse events were comparable between treatment groups. Hydromorphone ER was noninferior to oxycodone CR in alleviating cancer pain and was well tolerated.**

Perspective: ***This article demonstrates clinical noninferiority of the efficacy of once-daily hydromorphone ER compared with twice-daily oxycodone CR in alleviating cancer pain in Chinese patients, with comparable safety profiles between the 2 treatment groups. Thus, a treatment option with the potential for a reduced dosing frequency exists for health care providers and patients.***

Key words: *Brief Pain Inventory, cancer pain, hydromorphone extended-release, oxycodone, strong opioids.*

Chronic moderate to severe pain is an inevitable symptom associated with advanced stages of cancer; hence, alleviation of cancer pain is attributed prime importance in the World Health Organization (WHO) palliative care definition.[18] Morphine is the most commonly used strong opioid analgesic in the treatment of moderate to severe cancer pain. However, other strong opioids such as hydromorphone and oxycodone can be used as alternatives.[3,21] Hydromorphone is a hydrogenated semisynthetic ketone of morphine that exerts its analgesic effects through μ-opioid receptors in the central nervous system.[19] Per milligram, orally

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administered hydromorphone is approximately 5 times more potent than orally administered morphine.[15,22] Being a pure μ-opioid agonist, hydromorphone has no ceiling effect, and its maximum dose is based on the balance between efficacy and tolerability. For optimal pain control, opioids are to be administered "by the clock" and not "on demand" or "as needed."[3,16] However, frequent dosing is required for some opioid formulations, which may lead to poor adherence to therapy and thus result in inadequate analgesia and diminished quality of life.[4,9]

A once-daily extended-release (ER) hydromorphone hydrochloride formulation has been developed using OROS (oral osmotic therapeutic system) Push-Pull osmotic active technology (ALZA Corporation, Mountain View, CA) (hydromorphone ER).[8] This formulation is designed to release hydromorphone at a controlled rate for up to 24 hours for once-daily dosing and minimizes peak-trough plasma concentration fluctuations that are associated with the use of conventional immediate-release (IR) formulations.[8] Therapy can be initiated with hydromorphone ER, or patients can be switched from stable opioid therapies to hydromorphone ER without any loss of pain control.[11,13,17,23-25] Additionally, it reduces break-through pain (BTP) episodes and maintains the analgesia for long treatment periods in patients with chronic malignant and nonmalignant pain.[11,13,17,23-25] The safety and tolerability profiles of hydromorphone ER are consistent with other opioids, and the most commonly reported adverse events were nausea, constipation, somnolence, vomiting, headache, and dizziness for both cancer and noncancer pain.[7]

The other strong opioid alternative to morphine, oxycodone controlled-release (oxycodone CR), is a semisynthetic opioid analgesic. The recommended conversion ratio for oral oxycodone CR to oral morphine is 1:2.[2] As with hydromorphone ER, no ceiling effect is observed for treatment with oxycodone CR.[6] The oxycodone CR formulation used in this trial provides biphasic analgesia for 12 hours, with an immediate analgesic effect for 1 hour (38% of the dose) followed by a prolonged phase with a plasma half-life of 6.2 hours (62% of the dose).[14] Once-daily hydromorphone ER appears to have an efficacy and safety profile comparable to that of twice-daily oxycodone CR in the treatment of chronic noncancer pain.[1,10,20] Furthermore, the once-daily formulation of hydromorphone ER reduces the pill burden as compared with the twice-daily frequency of oxycodone CR formulation, which may facilitate better adherence to the therapy. However, there is lack of data on the comparison of these 2 treatments for the management of chronic cancer pain. Furthermore, there are no reports on the efficacy and safety of hydromorphone ER for pain treatment in the Chinese population. Thus, this randomized, double-blind, multicenter, comparative, parallel-group study aimed to investigate clinical noninferiority of efficacy of once-daily hydromorphone ER compared with twice-daily oxycodone CR for 28 consecutive days following completion of dose titration in Chinese patients with cancer pain.

Methods

Chinese patients aged 18 to 70 years (inclusive) who had inadequate control of moderate to severe cancer pain when receiving strong oral or transdermal opioid analgesics or who presented with cancer pain and were eligible to move to Step 3 of the WHO analgesic ladder when receiving weak opioids were included in the study. The study included patients who required or were expected to require between 40 and 184 mg of oral morphine or morphine equivalents every 24 hours for chronic management of cancer pain and those who were reasonably expected to achieve a stable dose of opioid study medication during the study. Required life expectancy of patients was 12 weeks or longer.

Patients were excluded from the study if they had pure neuropathic pain or pain of unknown origin (where a mechanism or physical cause could not be identified), only had pain on movement or acute pain, required other opioid analgesics (apart from morphine hydrochloride, in IR formulation, allowed as rescue medication for BTP), had any significant central nervous system disorder, and the risks of treatment with study medication could outweigh the potential benefits. Furthermore, women of childbearing potential who were pregnant or lactating were excluded from the study.

The independent ethics committee or institutional review board at each study site approved the protocol and the study was conducted in accordance with ethical principles based on the Declaration of Helsinki and that are consistent with International Conference on Harmonization (ICH) Guidelines of Good Clinical Practices and applicable regulatory requirements. All patients or their legally acceptable representatives provided written informed consent before entering the study.

Study Design

This was a phase 3, randomized, double-blind, multicenter, comparative, parallel-group registration study conducted to demonstrate the clinical noninferiority of efficacy of once-daily oral hydromorphone ER compared with twice-daily oral oxycodone CR in patients with moderate to severe cancer pain. The study sites were chosen according to the following criteria: investigator was a cancer pain specialist with previous clinical trial experience, sufficient human resources were available, recruitment rate estimation was reasonable, and equipment was available that could fulfill study requirements. The study consisted of 3 phases: a screening period (up to 14 days prior to randomization), a dose titration phase (up to 8 days), and a 28-day dose maintenance phase. Upon entry into the dose titration phase, randomized patients were converted from their prior opioids to their morphine equivalents (morphine to hydromorphone ER, 5:1; morphine to oxycodone CR, 2:1). Randomized patients were titrated to adequate effect (as determined by the pain assessments and supplementary analgesic requirements), and dosage adjustments were made no more frequently than every 2 days. Upward and downward dose titrations were allowed, but the maximum