The Oncologist®

Clinical Trial Results

Phase I/II Study of Weekly Oraxol for the Second-Line Treatment of Patients With Metastatic or Recurrent Gastric Cancer

Keun-Wook Lee,[a,b,*] Kyung Hee Lee,[c,*] Dae Young Zang,[d] Young Iee Park,[e] Dong Bok Shin,[f] Jin Won Kim,[a,b] Seock-Ah Im,[b] Sung Ae Koh,[c] Kyung-Sang Yu,[g] Joo-Youn Cho,[g] Jin-A Jung,[h] Yung-Jue Bang[b]

[a]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [b]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; [c]Department of Internal Medicine, Yeungnam University Hospital, Daegu, Republic of Korea; [d]Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea; [e]Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea; [f]Department of Internal Medicine, Gachon University Gil Hospital, Incheon, Republic of Korea; [g]Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [h]Clinical Research Team, Hanmi Pharmaceutical Co., Ltd., Seoul, Republic of Korea

*Contributed equally.

Access the full results at: Bang-15-202.theoncologist.com

Author Summary

Lessons Learned

- Oraxol, a novel oral formulation of paclitaxel, displayed modest efficacy as second-line chemotherapy for gastric cancer.
- Considering its favorable toxicity profiles, further studies are warranted in various solid tumors including gastric cancer.

Abstract

Background. Oraxol consists of paclitaxel and HM30181A, a P-glycoprotein inhibitor, to increase the oral bioavailability of paclitaxel. This phase I/II study (HM-OXL-201) was conducted to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of Oraxol. In addition, we investigated the efficacy and safety of Oraxol as second-line chemotherapy for metastatic or recurrent gastric cancer (GC).

Methods. In the phase I component, paclitaxel was orally administered at escalating doses (90, 120, or 150 mg/m^2 per day) with a fixed dose (15 mg/day) of HM30181A. Oraxol was administrated 6 times per cycle (days 1, 2, 8, 9, 15, and 16) every 4 weeks. In the phase II component, the efficacy and safety of Oraxol were evaluated.

Results. In the phase I component, the MTD could not be determined. Based on toxicity and pharmacokinetic data, the RP2D of oral paclitaxel was determined to be 150 mg/m^2. In the phase II component, 4 of 43 patients (9.3%) achieved partial responses. Median progression-free survival and overall survival were 2.6 and 10.7 months, respectively. Toxicity profiles were favorable, and the most common drug-related adverse events (grade ≥3) were neutropenia and diarrhea.

Conclusion. Oraxol exhibited modest efficacy and favorable toxicity profiles as second-line chemotherapy for GC. ***The Oncologist*** 2015;20:896–897

Discussion

Paclitaxel has been administrated intravenously because of its poor oral bioavailability. Because paclitaxel is insoluble in water, the original formulation of paclitaxel contains the vehicle Cremophor EL (CrEL); however, the addition of CrEL causes hypersensitivity reactions and exerts an additive effect on paclitaxel-induced neuropathy. The original formulation of paclitaxel inconveniences patients and increases the risk of toxicities. Consequently, there have been many efforts to develop a new formulation of paclitaxel.

Oraxol is composed of a paclitaxel capsule and an HM30181A tablet (Hanmi Pharmaceutical Co. Ltd., Seoul, Republic of Korea, http://www.hanmipharm.com). HM30181A, [2-(2-{4-[2-(6,7-dimeth,oxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenyl}-2*H*-tetrazol-5-yl)-4,5-dimethoxyphenyl]amide, is a novel inhibitor of P-glycoprotein in the gastrointestinal mucosa. In this phase I/II

ClinicalTrials.gov Identifier: NCT01491217
Sponsor(s): Hanmi Pharmaceutical Co., Ltd., Seoul, Republic of Korea
Principal Investigator: Yung-Jue Bang
IRB Approved: Yes

Correspondence: Yung-Jue Bang, M.D., Ph.D., Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Republic of Korea. Telephone: 82-2-2072-2390; E-Mail: bangyj@snu.ac.kr Received May 7, 2015; accepted for publication June 3, 2015; published Online First on June 25, 2015. http://dx.doi.org/10.1634/theoncologist.2015-0202

Table 1. Efficacy results of the phase II component

Efficacy parameters ($n = 43$[a])	Results
Tumor response to Oraxol, *n* (%)	
Complete response	0 (0.0)
Partial response	4 (9.3)
Stable disease	17 (39.5)
Progressive disease	20 (46.5)
Not evaluable	2 (4.7)
Overall response rate, % (95% CI)	9.3 (2.6–22.1)
Disease control rate, % (95% CI)	48.8 (33.3–64.5)
Progression-free survival, months, median (95% CI)	2.6 (1.7–3.5)
Overall survival, months, median (95% CI)	10.7 (7.2–14.2)

[a]Among 43 patients who were evaluated for efficacy, 2 patients underwent an unplanned tumor response evaluation using CT. These 2 patients did not undergo the planned CT evaluation at 8 weeks (2 cycles after the initiation of Oraxol treatment), but they were included in the efficacy evaluation.
Abbreviations: CI, confidence interval; CT, computed tomography.

study (HM-OXL-201), both paclitaxel and HM30181A were administered simultaneously on an empty stomach.

In the phase I component of this study ($n = 10$), no dose-limiting toxicity was observed, and thus the MTD could not be determined. In gastric cancer cell lines, paclitaxel exhibited cytotoxicity at concentrations >0.01 μM. In the pharmacokinetic analysis, the means of $T_{>0.01}$ (time of plasma concentration of paclitaxel >0.01 μM) at three paclitaxel dose levels were 17.7, 43.2, and 47.5 hours, respectively. The area under the plasma concentration-time curves also increased according to the paclitaxel dose. Based on these toxicity and pharmacokinetic data, dose level 3 (oral paclitaxel 150 mg/m^2 per day and HM30181A 15 mg/day, both on days 1, 2, 8, 9, 15, and 16 every 4 weeks) was determined as the RP2D.

In the phase II component ($n = 46$), this weekly Oraxol regimen displayed favorable toxicity profiles. The incidence of severe neutropenia (grade $\geq$3) was 30.4%, which was similar to that reported in previous phase III trials of conventional weekly paclitaxel (second line) in metastatic or recurrent GC. Severe nonhematologic toxicities were rare. Particularly, Oraxol appears to cause less peripheral neuropathy than conventional weekly paclitaxel. In our study, weekly Oraxol was associated with a response rate (RR) of 9.3% and progression-free survival (PFS), and overall survival (OS) of 2.6 and 10.7 months, respectively (Table 1). Statistically, our study did not meet the primary endpoint (RR); however, clinically, Oraxol appears to have efficacy similar to other cytotoxic agents commonly used as second-line chemotherapy in metastatic or recurrent GC. Regarding conventional weekly paclitaxel, RRs of 9%–20.9% and PFS and OS of 2.9–4.4 and 7.4–9.5 months, respectively, were reported. Although weekly Oraxol treatment did not meet the primary endpoint in this study, we demonstrated that Oraxol has its own advantages (favorable safety profiles, including less neuropathy and no hypersensitivity reactions, and the convenience of oral administration) over conventional paclitaxel. Consequently, we believe that Oraxol is worthy of further investigation. In particular, the combination of Oraxol with various chemotherapeutic agents is expected to be very promising because Oraxol displayed favorable toxicity profiles.

Author disclosures available online.