Oral paclitaxel with encequidar compared to intravenous paclitaxel in patients with advanced cancer: a randomised crossover pharmacokinetic study.

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Abstract

Background and purpose: Paclitaxel is a widely used anti-neoplastic agent but has low oral bioavailability due to gut extrusion by P-glycoprotein (P-gp). Oral paclitaxel could be more convenient, less resource intensive, and more tolerable than intravenous administration. Encequidar (HM30181A) is a novel, minimally absorbed gut specific P-gp inhibitor. We tested whether administration of oral paclitaxel with encequidar (oPac+E) achieved comparable AUC to intravenous paclitaxel (IVP) 80mg/m2. Experimental approach: We conducted a multi-centre randomised crossover study with two treatment periods. Patients (pts) with advanced cancer received either oral paclitaxel 615mg/m2 divided over three days and encequidar 15mg orally one-hour prior, followed by IVP 80mg/m2, or the reverse sequence. PK blood samples were taken up to day 9 for oPac+E and day 5 for IVP. Key Results: 42 pts were enrolled; 35 completed both treatment periods. AUC0-[?]was 5033.5 +/- 1401.1 ng.h/mL for oPac+E and 5595.9 +/- 1264.1 ng.h/mL with IVP. The geometric mean ratio (GMR) for AUC was 89.5% (90% CI 83.9-95.5). Mean absolute bioavailability of oPac+E was 12%. PK parameters did not change meaningfully after 4 weeks administration of oPac+E in an extension study. G3 treatment emergent adverse events occurred in 7 (18%) pts with oPac+E and 2 (5%) with IVP. 75% of pts preferred oPac+E over IVP. Conclusion and Implications: GMR for AUC was within the predefined acceptable range of 80%-125% for demonstrating equivalence. oPac+E is tolerable and there is no evidence of P-gp induction with repeat administration. With further study, oPac+E is a candidate to replace IVP.

Introduction

Taxanes are a class of commonly used chemotherapy compounds, originally identified from *Taxus* plants. The classical taxanes docetaxel and paclitaxel are widely used anti-neoplastic agents with activity in multiple solid tumours including breast (Ghersi et al., 2015), ovarian (Clamp et al., 2019), lung (Masters et al., 2015), and gastric cancer (Lu et al., 2018), as well as Kaposi and angiosarcoma (Rowinsky, 1997). Newer taxanes include cabazitaxel (De Bono et al., 2010) and the nanoparticle-bound nab-paclitaxel (H. Lee et al., 2020). The principal mechanism of action is thought to be disruption of microtubule function. Microtubules are essential for cell division and taxanes stabilize the GDP-bound tubulin in the microtubule, causing inhibition of cell division. Paclitaxel was first discovered in 1963 as part of an National Cancer Institute funded drug candidate screening programme, with activity in mouse models noted in 1978 (Walsh & Goodman, 2002; Wani, Taylor, Wall, Coggon, & McPhail, 1971). Its wide utility has resulted in it being listed on the WHO essential medicines list. The development of paclitaxel was initially hindered by insolubility in water, thus it is administered with the formulation vehicle cremophor EL (in a 1:1 mixture with dehydrated ethanol), which greatly increases the rate of hypersensitivity reactions. Paclitaxel is administered in a variety of dosage regimens as monotherapy or combination, frequently as a weekly infusion at a dose of 80mg/m^2 (Joerger, 2016). Patients are required to have repeated venepuncture, and the schedule uses expensive and often scare hospital infusion resources as well as valuable patient time.

Oral administration may improve convenience and have the potential to reduce costs. During COVID-19 global pandemic, oncologists are substituting oral for intravenous agents to reduce the number of patients' clinic visits and the inherent risks of exposure to SARS-CoV-2, without compromising oncological outcome(Schrag, Hershman, & Basch, 2020) (Hence, whenever possible, utilization of oral therapy regimens is recommended instead of intravenous anticancer therapies, if considered equivalent(Gosain et al., 2020).

Paclitaxel has low oral bioavailability due to structural instability in the gastrointestinal tract, active extrusion from enterocytes by p-glycoprotein (P-gp) and first pass metabolism by the liver enzymes CYP3A4 and CYP2C8(Jibodh, Lagas, Nuijen, Beijnen, & Schellens, 2013) (Schellens et al., 2000) (Kartner, Riordan, & Ling, 1983) (Helgason et al., 2006). Paclitaxel absorption is enhanced in P-gp and CYP knockout mice. Preclinical studies have evaluated combinations of Cyclosporine A, a known P-gp inhibitor and substrate for CYP3A4, and oral paclitaxel and showed a 13 fold increase in the oral bioavailability in mice(van Asperen, van Tellingen, van der Valk, Rozenhart, & Beijnen, 1998). Subsequently, Phase 1 and 2 studies investigated oral paclitaxel combination with cyclosporine A and showed promising results(Helgason et al., 2006; Malingré et al., 2000), however repeated use of cyclosporine A could also lead to serious adverse events such as hypertension and nephrotoxicity Investigation into other P-gp inhibitors such as elacridar and GF120918 have been commenced but not developed for routine use in the clinical setting.

Therefore more specific P-gp inhibitors have been developed such as HM30181A (encequidar; Hanmi Pharmaceutical; Seoul, Korea) (I. B. Paek, H. Y. Ji, M. S. Kim, G. Lee, & H. S. Lee, 2006; I. B. Paek, H. Y. Ji, M. S. Kim, G. S. Lee, & H. S. Lee, 2006). Encequidar is a novel, poorly absorbed, potent, selective gut specific p-glycoprotein inhibitor. Due to low oral bioavailability, the effects of Encequidar are limited to the intestinal enterocyte. In healthy volunteer studies, encequidar was well tolerated with no serious adverse effects at doses ranging from 180mg to 900mg in a single dose, and 60mg to 360mg doses daily for 5 days, with the maximum tolerated dose not reached.(Kim et al., 2012)

In a phase 1 study 24 patients received escalating doses of oral paclitaxel with encequidar (oPac+E, previously also known as Oraxol) to determine the maximum tolerated dose (DLTs)(H. J. Lee et al., 2014). In this study, the dose of paclitaxel was escalated from 60 to 420 mg/m^2 and the dose of encequidar from 30 to 210 mg/m^2 (half the dose of paclitaxel). The drugs were administered on days 1, 8 and 15 of each 28 day cycle. No premedication for hypersensitivity was delivered. Only one patient experienced a DLT (grade 3 neutropenia) at 240mg/m^2 of paclitaxel. The MTD was not reached in this study but maximum plasma concentration of paclitaxel was obtained at a dose level of 300 mg/m^2.

In another phase I / II study with oPac+E, paclitaxel was orally administered at escalating doses (90, 120 or 150 mg/m^2) with a fixed dose (15 mg/day) of encequidar(K. W. Lee et al., 2015). oPac+E was administered 6 times per cycle (day 1, 2, 8, 9, 15 and 16) every 4 weeks. In the phase 1 component of the study (n=10),

the MTD could not be determined but based on toxicity and pharmacokinetic data, the recommended phase 2 dose of oral paclitaxel in this 2 consecutive day schedule was determined to be 150 mg/m^2 per day.

In contrast to a dose escalation approach to determining optimal dosing schedule, we adopted a pharmacokinetic (PK) driven approach comparing the PK profile of sequential oral doses of oPac+E to the profile of IV paclitaxel. In a pilot pharmacokinetic study, we enrolled patients with advanced cancer who were scheduled to receive oPac+E and compared IV administration of paclitaxel with oPac+E(Jackson et al., 2016). Three cohorts were enrolled with escalating oral paclitaxel doses of 270mg/m^2 (6 patients), 274mg/m^2 (2 patients) or 313mg/m^2 (2 patients) daily over two consecutive days, preceded by Encequidar 15mg (fixed dose). With a two-day dosing schedule saturation at 274mg/m^2 was observed. PK modelling predicted a three-day schedule of 205mg/m^2 per day could achieve bioequivalence between oPac+E and IV paclitaxel 80mg/m^2

To test this hypothesis, we undertook a multicenter, open label, 2 stage study with a 2-treatment period crossover design to test whether oPac+E achieved comparable exposure by AUC to IV paclitaxel 80mg/m^2. We also undertook an extension study to test safety of repeated administration of oPac+E, with repeat PK after 4 weeks administration to test whether potential accumulation or P-gp/CYP induction occurred that may affect systemic concentrations and potentially diminish efficacy.

Methods

Study oversight

The study was listed on the Australian New Zealand Clinical Trials Registry website (15/STH/87), approved by the independent ethics committee at each participating institution and conducted in accordance with standard operating procedures of the Sponsor which were designed to ensure adherence to Good Clinical Practice (GCP) guidelines. All the patients provided written informed consent before enrolment into the study.

Eligibility criteria

Participants were required to have advanced cancer; be scheduled to receive weekly paclitaxel 80mg/m^2 as monotherapy or in combination with other agents; provide written informed consent; age >/= 18, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1, and have life expectancy of 3 months or more. Other key inclusion criteria were: adequate bone marrow reserve (Hb >/= 90g/L, neutrophil count >/= 1.5x10^9/L, platelet count [?]100 x 10^9/L), hepatic reserve (total bilirubin of [?]20 μmol/L or, for subjects with liver metastasis, [?]30μmol/L; alanine aminotransferase (ALT) [?]3 × upper limit of normal (ULN) or, for subjects with liver metastasis, [?]5 x ULN; alkaline phosphatase (ALP) [?]3 x ULN or, for subjects with liver or bone metastasis, [?]5 x ULN, gamma glutamyl transferase (GGT) <10 x ULN), and adequate renal function (calculated creatinine clearance > 50ml/min by Cockcroft-Gault, or Cr <177 μmol /L), willing to fast 8h prior and 4 hour post dose, and refrain from alcohol and caffeine. Concomitant inducers or inhibitors of P-gp or CYP 3A4 or 2C9 were prohibited within 2 weeks of study medicine.

Study design and treatment

The was a multi-centre, open-label study with randomised cross-over design. There were two treatment periods: in the oPac+E treated group, patients were to receive encequidar 15mg daily for three days a week and oral paclitaxel 615mg/m^2 divided over 3 days with rounding to the nearest 30mg capsule. At the completion of the two treatment periods, patients were eligible to return to usual care with weekly paclitaxel, or enter into an extension study of oPac+E three days per week at the dose administered in the current study. The encequidar tablet was administered 1 hour before the oral paclitaxel capsules. In the IV paclitaxel group, patients received weekly Taxol® 80mg/m^2 IV infused over one hour. Patients were randomised by computer generated central randomization scheme to receive oPac+E followed by IV Taxol, or the reverse sequence. Subjects were instructed to fast for at least 8 hours before and 4 hours after oPac+E dosing.

Intravenous paclitaxel was administered according to standard local practice. oPac+E was administered in an inpatient clinical research unit. Patients receiving IV PAC were administered standard prophylactic

steroids and antihistamines. No premedication was allowed before the first dose of oPac+E; in the follow-up extension study premedication was permitted before subsequent doses for hypersensitivity reactions and/or nausea or vomiting. Intensive blood sampling was undertaken for the first 3 days while on oPac+E, with samples taken pre-dose, after dosing (0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, and 18 hours), on Day 2 to Day 5 or 9 to Day 12, samples were taken predose, after dosing (0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 32, 48, 56, 72, 96, 120 and 144 hours). With Taxol® administration blood sampling was performed pre-dose, during infusion (2, 5, 8, 12, 20, 40, and 60 minutes), after infusion (0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, and 24 hours, then at 32, 48, 56, 72 and 96 hours post dose. Standard baseline investigations were performed including physical exam, ECG, pregnancy test in pre-menopausal female subjects, haematology and biochemistry samples, and urinalysis. After completing both treatment periods patients were asked which treatment they preferred. Adverse events were collected and graded according to CTCAE 4.03, and causality assessed by investigators.

Bioanalytical Methods

Plasma concentrations of paclitaxel were measured using a validated liquid chromatography/mass spectrometry/ mass spectrometry assay with a lower limit of quantification of 2.5 ng/mL.

Data and Statistical analysis

Statistical analyses were reported using summary tables, graphs, and data listings. Continuous variables were summarized using the N, mean, SD, median, minimum, and maximum. Summaries of PK parameters also included the geometric mean and the coefficient of variation. Categorical variables were summarized by counts and by percentage of subjects in corresponding categories. All raw data obtained from the electronic case report form (eCRF), as well as any derived data, were included in data listings.

Pharmacokinetic Analyses

All subjects who received both study treatments, completed scheduled posttreatment PK evaluations, and were protocol compliant were included in the PK analysis set. Subjects who vomited within twice the median T_{max} were excluded from the primary analysis.

Paclitaxel plasma concentrations were normalized to 615mg/m^2 for oPac+E and 80 mg/m^2 for IV paclitaxel. Pharmacokinetic and statistical analyses were based on normalized plasma concentrations. Plasma concentrations for paclitaxel were analysed to determine the following PK parameters by noncompartmental analysis using plasma concentration time data for oral and IV paclitaxel: $AUC_{0\text{-}[?]}$ (primary endpoint) as well as C_{max}, $AUC_{0\text{-}t}$, T_{max}, and $t_{1/2}$ (secondary endpoints).

The equivalence of the extent of exposure was determined by comparing the $AUC_{0\text{-}[?]}$ of the selected dose of oral paclitaxel (as oPac+E) (administered over 3 consecutive days) to the $AUC_{0\text{-}[?]}$ of IV paclitaxel.

The primary PK parameters were compared between IV paclitaxel (reference) and oral paclitaxel (test) formulations. Analysis of variance (ANOVA) was performed (α=0.05) on the untransformed and log10 transformed PK parameters C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}[?]}$ for paclitaxel. The ANOVA model included sequence, subjects nested within the sequence, period, and formulation as factors. The significance of the sequence effect was tested using the subjects nested within the sequence as the error term. Two-sided 90% CIs for the log transformed ratio of test/reference of the least squares means obtained from the ANOVA for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}[?]}$ were estimated. Equivalence was to be concluded if the 90% CI of the ratio (oral paclitaxel 615mg/m^2 over 3 consecutive days [oPac+E] / 80 mg/m^2 IV paclitaxel) of the least square means from the ANOVA of the log-transformed $AUC_{0\text{-}[?]}$ was within the 80% to 125% acceptance range.

Safety Analyses

For treatment emergent adverse events (TEAEs), verbatim terms were mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; version 20.0); CTCAE v4.03 was used to grade severity. Incidences of TEAEs were displayed by SOC and PT, and summarized by treatment, treatment period, and treatment sequence. Treatment emergent AEs and

SAEs were listed with start and end dates (unless ongoing), severity, relationship to study drug, study drug action taken, and outcome by subject. Laboratory evaluations were summarized and evaluated for markedly abnormal values based on the normal range; shift tables from baseline to posttreatment were also provided for select parameters. Results from ECGs and ECOG Performance Status were summarized. Vital signs, physical examination findings, and treatment preference were listed by subject. Treatment preference was summarized and listed.

Sample Size Rationale

It was planned to enrol an initial cohort of up to 6 patients with an oPac+E dosing regimen consisting of oral encequidar 15 mg plus an oral paclitaxel dose of 615mg/m^2 divided over 3 consecutive days taken in once daily doses. An interim analysis of pharmacokinetic (PK) data was conducted to determine the intrasubject variability and geometric mean ratio (GMR) for $AUC_{0\text{-}[?]}$. If it appeared likely that the selected regimen could meet the criteria for BE based on $AUC_{0\text{-}[?]}$, additional subjects would be enrolled in Stage 2 at this dose. Based on this pre-planned interim analysis, an additional 34 evaluable subjects were enrolled into Stage 2. A total sample size of 40 evaluable subjects was projected to provide 90% power for the 90% CI of the geometric mean ratio for $AUC_{0\text{-}[?]}$ to fall in the range of 80% to 125%.

Protocol amendments

During the study, the protocol was amended to allow extended treatment delay or interruption between treatment periods to permit recovery from toxicity or other reason, lowered Hb eligibility threshold from 100g/L to 90g/L, and added inclusion criteria of gamma glutamyl transferase $<10 \times$ ULN to demonstrate adequate liver function based on emerging safety data from other ongoing studies of oPac+E. Other changes were non-substantive.

Results

Recruitment

The study was conducted at 3 sites in New Zealand, 1 site in Australia, and 3 sites in Taiwan between 26 Aug 2015 and 27 Mar 2019. 6 patients were recruited at one site (Dunedin, NZ) into the first cohort. Based on interim safety and PK data, it was elected to recruit 34 further patients at the same dose schedule.

In total, a total of 42 subjects were randomised, two participants experienced AEs prior to receiving any study drug and were withdrawn, and 40 subjects received study drug (37 received both OPE and IV paclitaxel, 2 received OPE only, and 1 received IV paclitaxel only). Two patients who received both treatments collected IV PK samples only up to the end of infusion and hence were incomplete regarding PK assessment. As such, 40 participants were considered for the safety analysis, and 35 were included for the PK analysis set (see fig 1 for further detail).

Baseline characteristics

The median age was 59 years (range 32-78), with the majority of subjects being female 65% and Caucasian 73%. Demographic and tumour characteristics are listed in Table 1.

PK data

Derived paclitaxel PK parameters are summarized in Tables 2 and 3 and Figure 2. Following administration of paclitaxel, mean time to peak concentration was approximately 1 hour post oral and IV dosing (figure 2). Mean terminal $t_{\frac{1}{2}}$ was longer with oral dosing (43 hours) than after IV administration (26 hours). Mean C_{max} following oral administration of paclitaxel was one-seventh of that following IV administration. For oral administration, $AUC_{0\text{-}[?]}$was 5033.5 +/- 1401.1 ng.h/mL compared to 5595.9 +/- 1264.1 ng.h/mL with IV. The intrasubject coefficient of variation was 16.1%. Based on log transformed data, the geometric mean ratio (GMR) for AUC was 89.5% (90% CI 83.9-95.5). The 90% CI was within the predefined acceptable range of 80% to 125% for demonstrating bioequivalence. The mean absolute bioavailability of oral compared

to IV paclitaxel was 12%. There was no difference in bioavailability or AUC by Asian compared to European ethnicity (Figure 3).

Toxicity

Toxicity is summarised in table 4. At least 1 treatment emergent adverse event (TEAE) was reported in 38 (95%) Safety Analysis Set subjects. More subjects reported TEAEs during oPac+E treatment (36 [92%] subjects) than during IV paclitaxel treatment (29 [76%]). Grade 3 TEAEs were reported in 8 (20%) subjects, inclusive of 7 (18%) subjects during oPac+E treatment and 2 (5%) subjects during IV paclitaxel treatment. Serious TEAEs were reported in 6 (15%) subjects and were judged treatment-related by the Investigator in 2 (5%) subjects, both of whom were during oPac+E treatment. Three (8%) subjects had at least 1 TEAE resulting in discontinuation of study drug (1 [3%] during oPac+E treatment and 2 [5%] during IV paclitaxel treatment) and 2 (5%) subjects discontinued from the study due to a TEAE (both during IV paclitaxel treatment). One subject died 26 days after her last dose of on-study IV paclitaxel.

Thirty (75%) subjects preferred oPac+E treatment over IV paclitaxel, while IV paclitaxel was preferred over oPac+E in 6 (15%) subjects. No treatment preference was reported in the remaining 4 subjects.

Discussion and Conclusions

Paclitaxel is a widely used anti-neoplastic agent and weekly schedules are now in common usage. This however results in considerable consumption of health care resources, and precious patient time. Oral formulations have several potential advantages but their development is complex. Paclitaxel is poorly absorbed due to active extrusion by P-gp and undergoes extensive first pass metabolism. The combination with a gut-specific P-gp-inhibitor is a rational approach to improve bioavailability. Previous work has shown saturation at doses of paclitaxel above 300mg/m^2 with once daily dosing. Other P-gp inhibitors have been trialled, but have not progressed due to either toxicity of the inhibitor, or failure to achieve comparable exposure.

The classical MTD approach to drug development may not be ideal when developing oral versions of agents with well-established dosing schedules and known therapeutic effects. Several other studies have taken an MTD approach but have achieved saturation which may compromise therapeutic drug exposure.

We took a PK-directed approach to develop a schedule that could potentially achieve similar exposure, measured by AUC, as IV paclitaxel 80mg/m^2.

Unsurprisingly, the C_{max} of paclitaxel with oPac+E is lower than with IV. However, with multi-day dosing we were able to demonstrate AUC of paclitaxel with oPac+E was comparable within the prespecified bounds compared to IV administration, meeting the study primary endpoint.

We found no difference in oral bioavailability between Asian and European patients, and PK profile was consistent after 4 weeks exposure to oPac+E suggesting that there is no clinically relevant induction of P-gp or CYP enzymes. This implies that prolonged treatment will not result in meaningful reductions in drug exposure.

The mean terminal half-life was longer with oral exposure than IV, suggesting either ongoing oral absorption, or that IV clearance differs, possibly mediated by cremophor.

Several challenges remain. This study was designed to measure PK profile and it is not possible to determine, from this study, the safety profile of prolonged administration. This is important as lower Cmax could impact on toxicity profile such as the incidence of alopecia, or the development of neuropathy. We found that oPac+E was adequately tolerated in the three-day schedule but further study will be required to establish the full safety profile with repeat dosing.

Our study used strict fasting requirements with patients fasting 8 hours prior and 4 hours after administration. This provided ideal conditions for studying PK parameters however is unlikely to be feasible in routine clinical practice. Food studies are required.

The oral formulation also uses slightly less than 8 times the raw amount of paclitaxel for oral dosing compared to IV administration. This does have potential consequences for manufacture and supply for such a widely used anti-neoplastic.

The schedule we devised in this study has been taken forward for further study, which has recently completed. That study enrolled 402 patients with metastatic breast cancer and randomised patients in a 2:1 ratio to receive our schedule of oPac+E or IV Paclitaxel at the registration dose of 175mg/m^2 Q3W. The Oral schedule achieved higher response rate (primary end-point) and numerically longer median OS (27.9 months v 16.9 months, study not powered for OS). Toxicities were much less in oral group, with only 1% of patients experiencing grade 3 polyneuropathy (PNP), versus 8% in the IV group (all grades PNP 17% versus 57%). The much lower incidence and severity of neuropathy could be a major advantage in the treatment of cancer patients. Additionally, fewer patients experienced alopecia, but slightly more patients had GI disturbance or neutropenia. (Umanzor et al., 2020)

In conclusion, we found that a combination of oral paclitaxel 205mg/m2 and encequidar 15mg in a three-day schedule is equivalent on AUC to paclitaxel 80mg/m^2 and provides advantages to cancer patients over traditional IV weekly paclitaxel. PK parameters after 4 weeks exposure were unchanged, indicating no evidence of induction of P-gp or CYP enzymes. There was no evidence of variation between Asian and European ethnicity. There were no concerning safety signals. Participants preferred oPac+E to IV paclitaxel. oPac+E may be a candidate to replace weekly IV paclitaxel subject to confirmatory safety and efficacy data.

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Figure 3 Box Plots of Paclitaxel AUC by Ethnicity