

History of Paclitaxel and Oral Paclitaxel – Clinical Data and Future

Paclitaxel

The most known natural source cancer drug is paclitaxel, which is derived from the tough protective outer sheath of the trunk and branches (referred as bark) of the Pacific yew tree (*Taxus brevifolia*).^[1] Paclitaxel has demonstrated a wide spectrum of antitumor activity as a single agent and also in combination with other chemotherapeutic agents as part of combination regimens.^[2] It is used extensively in the treatment of advanced carcinomas of the breast, ovarian cancer, nonsmall cell lung cancer, and other solid tumors.

Although discovered in 1962, development toward the clinic was slow, mainly due to the difficulties in harvesting paclitaxel and due to the complexities involved in synthesizing the compound. Polysciences, Inc. was the first company to achieve large-scale production of paclitaxel. Clinical trials with paclitaxel were initiated when it was made possible to derive 10-deacetylbaccatin III (a precursor of paclitaxel), from the plant which many people have in their gardens, namely *Taxus baccata*.^[1]

Paclitaxel also posed other challenges during its development. Due to its hydrophobic nature, formulation which can be administered to human beings was difficult. When the bulk drug was suspended to have a solution, initial cytotoxic activity was noted. Later to make the formulation acceptable for human use, paclitaxel was mixed with an ethanol, cremophor, and saline solution in the ratio 5:5:90 to a concentration of 0.3–0.6 mg/mL. With this, the intraperitoneal activity was maintained at the levels, which were noted earlier.^[1]

In 1984, the National Cancer Institute initiated first in human clinical trials of paclitaxel wherein patients with various cancer types. The spur in clinical demand followed the report wherein investigators at Johns Hopkins reported partial or complete response in 30% of patients with advanced ovarian cancer in 1989.^[1]

In December 1992, the United States Food and Drug Administration (US-FDA) approved the therapeutic use of paclitaxel in patients with ovarian cancer. In 1994, postconclusive evidence on the effectiveness of paclitaxel against advanced breast cancer, US-FDA approved paclitaxel in the treatment of breast cancer.^[1]

Formulations of Paclitaxel

During the development of paclitaxel, researchers noticed the difficulty of formulating it into a formulation, which can be easily administered to humans, mainly due to the hydrophobic nature of paclitaxel and to address this concern a cremophor-based formulation of paclitaxel was developed. But later, it came to the notice of the researchers that

cremophor is adding to the toxic effects of paclitaxel. The hypersensitivity reaction which is noted during the infusion of paclitaxel in 25%–30% of patients receiving it was contributed by cremophor.^[3,4] With an objective to control the incidence and severity of hypersensitivity reactions, a practice of using premedication with histamine 1 and 2 blockers and glucocorticoids like dexamethasone, were followed.^[5] It was noted that cremophor also contributes to other chronic toxic effects of paclitaxel, for example, peripheral neuropathy.^[6] An add-on issue of leaching of plasticizers due to ethanol and cremophor from infusion bags and infusion set made up of polyvinyl chloride (PVC) was noted.^[7] As a result, administration of paclitaxel was done using glass bottles or materials used of non-PVC material and using in-line filters. All these issues developed need for paclitaxel formulations with different solvents and improved solubility.^[8]

Abraxis Biosciences developed a protein-bound paclitaxel injectable formulation of paclitaxel. This formulation used albumin as a delivery vehicle for paclitaxel. This formulation was approved by US-FDA in year 2005 with brand name Abraxane. The use of nanoparticle albumin-bound technology with albumin as a vehicle was first in class drug wherein albumin (human protein) was used to deliver the chemotherapy. Abraxane did not contain solvents like cremophor, and hence the mandatory requirement of premedication with antihistamines or steroids was excluded from the study.

Many Indian generic pharmaceutical companies are developing generic formulation of Abraxane. Few of the companies have also launched the generic or modified formulations of paclitaxel in the Indian market.

Background of Oral Paclitaxel

The challenges such as anaphylactic reactions to cremophor, requirement of medication with steroid, hospital visits for administration of chemotherapy, and costs associated with intravenous (IV) administration of paclitaxel developed thoughts toward oral paclitaxel. The key hurdle in the development of oral paclitaxel is poor oral absorption of paclitaxel due to its active excretion by P-glycoprotein (P-gp) in the intestinal cells. Athenex, USA, has developed “Oraxol,” which is an oral paclitaxel and HM30181 (encequidar), a novel oral inhibitor of intestinal P-gp which enables the oral administration of paclitaxel.^[9] Encequidar possesses inhibitory activity specific against P-gp and has minimal oral absorption. This distinguishing characteristic of encequidar limits its inhibitory action locally to the luminal endothelium of gastrointestinal tract and thus improves the absorption of paclitaxel.^[10] No other interaction is reported between paclitaxel and encequidar.

There is another formulation of oral paclitaxel which is in clinical development. DHP107 is being tested in patients with recurrent and metastatic breast cancer (MBC). The ongoing Phase 2 trial with this molecule is registered on ClinicalTrials.gov (NCT03326102). The trial is expected to recruit 72 patients in 2:1 ratio wherein patients will be randomized to either DHP107 at dose of 200 mg/m² orally twice daily on days 1, 8, and 15 every 28 days or IV paclitaxel 80 mg/m² weekly (3 weeks on/1 week off). At the time of writing this article, the study status is recruiting and expected to have a primary completion date of September 2020 and the study completion date of April 2022.^[11] It would be interesting to know the results of the trial, although another oral paclitaxel therapy is much in advanced stage of development.

Clinical Development of Oral Paclitaxel-Oraxol

Pharmacokinetic trial

The single-arm, open-label, multicenter, pharmacokinetic trial was conducted wherein oraxol (HM30181A at 15 mg plus oral paclitaxel 205 mg/m²) was administered orally for 3 consecutive days, every week for up to 16 weeks.^[9] In this trial, pharmacokinetic parameters for oral paclitaxel were characterized at week-1 and week-4, tumor response was evaluated at weeks 8 and 16 using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and toxicity profile was assessed using Common Terminology Criteria for Solid Tumors version 4.03.

A total of 28 MBC patients were enrolled in this trial, with a mean age of 56.6 years (range: 38–79 years). Of 28 patients enrolled in the trial, 26 patients had failed multiple previous chemotherapies. Of 26 evaluable patients, oraxol demonstrated partial response in 11 (42.3%) patients, stable disease in 12 (46.2%), and progressive disease in 3 (11.5%) patients. Treatment-related serious adverse events (grade ≥ 3 neutropenia) were observed in three patients, and all patients recovered completely. Pharmacokinetic parameters showed that the area under the curve of oraxol with paclitaxel as analyte at week-1 was reproducible at week-4 (3050–3594 ng-h/mL).

The trial concluded that the antitumor activity demonstrated by oraxol in MBC patients who have failed previous chemotherapies is encouraging with acceptable toxicity profile.

Comparative Phase 3 trial

The Phase 3 study was conducted in 402 patients with metastatic breast cancer, with a primary objective of radiologically confirmed tumor response rate (RR) at 2 consecutive timepoints using RECIST v1.1, and safety/tolerability in enrolled patients and secondary objectives of progression-free survival (PFS) and overall survival (OS).^[12] The enrolled patients were randomly assigned to either 205 mg/m² of oral paclitaxel with encaequidar (oraxol) for

3 days a week or 175 mg/m² IV conventional paclitaxel every 3 weeks in a 2:1 ratio in favor of oraxol treatment group such that at the end of the study, 265 patients were assigned to oraxol, and 137 patients were assigned to IV paclitaxel treatment arm. The efficacy evaluation included assessment of tumors for response and confirmation at 2 consecutive evaluations by blinded, independent radiology assessments.

The study demonstrated that patients administered oraxol had a confirmed tumor RR of 35.8%, and the IV paclitaxel group had RR of 23.4%. The difference in RR between oraxol and IV paclitaxel group was 12.4% ($P = 0.011$). The prespecified modified intention to treat (mITT) analysis included 360 patients with 240 patients assigned to oraxol group and 120 patients assigned to IV paclitaxel group. This analysis excluded patients that did not have target lesions as per RECIST for central radiology evaluation or who did not receive adequate treatment. The RR noted per mITT analysis was 40.4% in oraxol group and 25.6% in IV paclitaxel group with a difference of 14.8% ($P = 0.0005$). Responses noted in the study were also more durable considering the median duration of confirmed response in oraxol treatment arm (39 weeks) than response noted in IV paclitaxel arm (30.1 weeks).

The ongoing analysis of PFS demonstrated a median PFS of 9.3 months for oraxol treatment arm and 8.3 months for IV paclitaxel treatment arm ($P = 0.077$). The OS analysis also demonstrated a difference in favor of oraxol (27.9 months) versus IV paclitaxel (16.9 months) ($P = 0.035$). The safety analysis between two treatment groups showed lower incidence of neuropathic risk with oraxol group (17%) as compared to IV paclitaxel group (57%). The severity of neuropathic symptoms was also lower in oraxol group (1% patients with grade 3 neuropathy) as compared to IV paclitaxel group (8% patients with grade 3 neuropathy).

Further, safety analysis demonstrated that patients with oraxol arm report higher rates of neutropenia, infection, and gastrointestinal adverse events as compared to IV paclitaxel arm; but these adverse events were of low grade.

The Theory of Oral versus IV Chemotherapy – the Capecitabine Experience

Another example of oral versus IV chemotherapy is capecitabine and 5-fluorouracil (5-FU). Capecitabine is tumor-activated prodrug of 5-FU, and it is administered orally. It was developed with an intention to reduce nontumor cytotoxicity profile and also to improve tolerability. On oral administration, capecitabine (which is inactive prodrug) is absorbed through the intestine and is converted in the liver to 5'-deoxy-5-fluorouridine (5'-DFUR). Further to this, 5'-DFUR is converted into the active form, that is, 5-FU by the enzyme thymidine phosphorylase in both normal and tumor tissue. The concentration of enzyme thymidine phosphorylase is higher within tumor cells.^[13] With this,

there is greater tumor targeting with decreased systemic exposure.

A meta-analysis comprising of 6171 patients with stomach, colon, and colorectal cancer of 6 phase 3 trials was conducted. The metanalysis concluded that the efficacy of oral capecitabine matches with that of IV 5-FU, and oral capecitabine can replace it in the treatment of stomach, colon, and colorectal cancer. This conclusion was presented at the 10th World Congress on Gastrointestinal Cancer in Barcelona, Spain, by Jim Cassidy, MD.^[14] Capecitabine-based neoadjuvant chemoradiotherapy has also shown improvement in pCR, ad R₀ resection, and nodal downstaging in patients with locally advanced rectal cancer when compared with 5-FU-based neoadjuvant chemoradiotherapy.^[15]

A pharmacoeconomic analysis of capecitabine and 5-FU was carried out by Cassidy *et al.*,^[16] wherein clinical effectiveness, chemotherapy costs, expenses toward managing adverse events, and costs for time and travel were assessed. The study showed that the average expenses toward medication for the management of adverse events was lower in the capecitabine treatment arm compared with the 5-FU/LV treatment arm (£86 and £345, respectively) and mean travel cost per patient was lower with capecitabine (£62) compared with 5-FU/LV (£196). Such analysis on pharmacoeconomic grounds denotes that the use of capecitabine versus 5-FU as adjuvant treatment in patients with colon cancer would help reducing the direct medical cost and help improving health outcomes compared with 5-FU/LV. The economic platform would term capecitabine “dominant,” as it will not only be cost saving but also more effective treatment.^[16]

Challenges Noted with Oraxol

The dosing schedule for the oraxol means that you cannot eat for 9 h. This happens for 3 days in a row each week.

This study compared oral paclitaxel to IV paclitaxel given every 3 weeks. We know now that giving IV paclitaxel every week offers the same benefits as every 3-week dose but causes fewer side effects. The results of this study only apply to IV paclitaxel given every 3 weeks. Hence, we do not know how oral paclitaxel compares to IV paclitaxel given every week.

Next Steps

Although head-to-head comparison of oral paclitaxel versus paclitaxel IV weekly administration is not conducted, current results of oral paclitaxel are very encouraging from efficacy and safety perspective. Oral paclitaxel has scored over IV paclitaxel in efficacy as well, but looking at the pharmacoeconomic example of capecitabine demonstrating safety advantage may also help in gaining popularity for oral paclitaxel versus IV paclitaxel upon its commercialization.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

**Ganesh Divekar¹, Bharat Bhosale^{2,3,4,5,6},
Padmaj Kulkarni⁷**

¹Clinical Operations and Medical Services, SIRO Clinpharm Pvt. Ltd., Thane, Maharashtra, India, ²Department of Medical Oncology, Bombay Hospital and Medical Research Centre, Mumbai, Maharashtra, India, ³Department of Medical Oncology, Vedant Hospital, Thane, Maharashtra, India, ⁴Department of Medical Oncology, Jaslok Hospital and Research Centre, Mumbai, Maharashtra, India, ⁵Department of Medical Oncology, Sir H N Reliance Foundation Hospital and Research Centre, Mumbai, Maharashtra, India, ⁶Department of Medical Oncology, SL Raheja Hospital, Mumbai, Maharashtra, India, ⁷Department of Medical Oncology, Deenanath Mangeshkar Hospital, Pune, Maharashtra, India

Address for correspondence:

Dr. Padmaj Kulkarni,
Department of Medical Oncology, Deenanath Mangeshkar Hospital,
Pune - 411 004, Maharashtra, India.
E-mail: padmaj.kulkarni@gmail.com

Submitted: 07-Apr-2020

Revised: 16-Apr-2020

Accepted: 23-Apr-2020

Published: 13-Jun-2020

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<p>Quick Response Code:</p> 	<p>Website:</p> <p>www.ijmpo.org</p> <hr/> <p>DOI:</p> <p>10.4103/ijmpo.ijmpo_139_20</p>

How to cite this article: Divekar G, Bhosale B, Kulkarni P. History of paclitaxel and oral paclitaxel – Clinical data and future. *Indian J Med Paediatr Oncol* 2020;41:260-3.