A fixed-dose combination treatment for late-stage breast cancer

Current treatment of metastatic breast cancer (MBC) aims to ameliorate symptoms and improve quality of life for patients. Intas Pharmaceuticals Ltd is forging the way ahead for MBC treatment with the world's first fixed-dose combination (FDC) of two known chemotherapy drugs: 'capecitabine' and 'cyclophosphamide'. This unique FDC formulation is based on patented tablet-in-tablet technology, which has been approved by the regulatory authorities in India based on THE ENCLOSE clinical trial. It is marketed by Intas as Comcapsy® (capecitabine 400/700 mg + cyclophosphamide 20/30 mg). The combined oral fixed-dose tablet provides the advantage of ease of dosing, better patient adherence, and a manageable tablet load for patients with breast cancer.

In India, breast cancer is the leading cause of cancer mortality, representing 11.1% of all cancer deaths. In this context, breast cancer mainly affects women of reproductive age, where its late diagnosis leads to a high mortality rate. When not treated promptly, breast cancer can result in the spread of disease from the breast to other organs and tissues, and is known as metastatic disease, or stage 4 breast cancer. The symptoms caused by metastatic breast cancer (MBC) depend on the site of metastasis. Common metastatic sites include the bones, liver, lungs, and brain.

Approximately half of patients with breast cancer in India are diagnosed in stages 3 and 4 when the chances of survival are significantly lower and treatment costs are high. Treatment is focused on palliation to offer relief from symptoms caused by the disease itself and by the aggressive cancer treatment. Although palliation helps the patient feel more comfortable and improves their quality of life, it does not cure the disease.

Currently, available treatments for breast cancer include surgery, radiation therapy, chemotherapy, hormonal therapy, and targeted therapy. Current chemotherapy medications for MBC include oral anticancer drugs, anthracyclines and/or taxanes. Within the body, the anticancer drug capecitabine is converted to 5-fluorouracil, a substance which blocks cancer cell multiplication and results in cancer cell death. Cyclophosphamide, besides slowing/stopping growth of cancer cells through the body's immune system, also enhances the conversion of capecitabine to active 5-fluorouracil, suggesting a collaborative activity of the two medications (known as synergistic anti-tumour activity).

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TABLET-IN-TABLET TECHNOLOGY

Through its patented tablet-in-tablet technology, Intas Pharmaceuticals Ltd has developed the first oral fixed-dose combination (FDC) tablet of capecitabine and cyclophosphamide. The FDC demonstrated promising results in THE ENCLOSE clinical trial recently published in the high-impact factor journal, *The Breast*. Following positive results from the trial, the combination treatment was marketed in India, after regulatory approval, in April 2020. The labelled dose of capecitabine alone can negatively impact the pill burden, and the addition of other oral drugs can further increase the tablet load, negatively affecting patients' treatment adherence. This oral FDC provides the advantage of ease of dosing and better adherence as well as manageable tablet load for patients with breast cancer.

THE ENCLOSE STUDY

THE ENCLOSE (capEcitabiNe CycLophOsphamide Synergism brEast cancer) study determined the efficacy and safety profile of the world's first oral FDC tablet of capecitabine and cyclophosphamide. In this randomised, multicentre study, patients with MBC who previously experienced failure of first-line treatment (with anthracyclines and/or taxanes) were included.

The study was conducted in two parts between February 2015 and November 2018 at 15 centres across India. Sixty-six women were initially randomised into three dose groups: D1, D2, and D3.

These doses were calculated after considering the scientific literature on the specific medications. The FDC tablets were administered orally within 30 minutes after a meal in a regimen of 14 days on and seven days off in three-weekly cycles for up to six cycles.

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Group D1 Received 1,400mg capecitabine and 60mg cyclophosphamide daily

Group D2 Received 1,800mg capecitabine and 80mg cyclophosphamide daily

Group D3 Received 2,200mg capecitabine and 100mg cyclophosphamide daily.

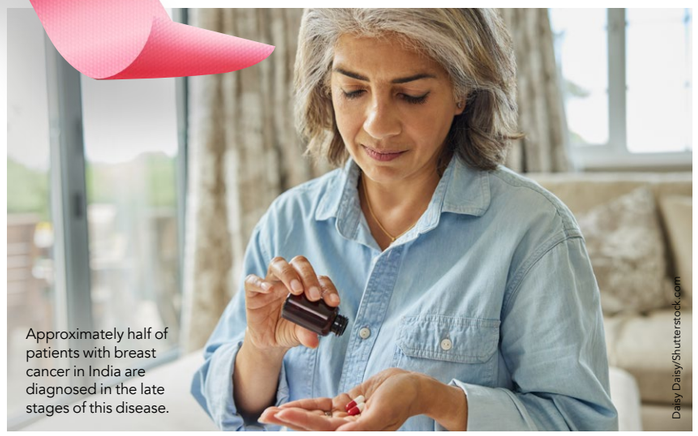
Part I of THE ENCLOSE Study

Being a novel formulation, detailed pharmacokinetic assessment of the FDC was included as part of the trial. Part I of the study focused on the pharmacokinetics – to investigate how the body interacts with the drugs. Blood samples were collected from patients and the concentration of the drugs in their blood was calculated at different time points. The pharmacokinetic profiles were evaluated in 24 out of 66 patients and did not reveal any concerning findings. Pharmacokinetic parameters were greater than dose proportional for capecitabine.

Following a futility analysis, D1 dose was not considered optimal and discontinued. With additional patients recruited in D2 and D3 groups, a total of 144 patients' data were available for analysis in part II of the study.

Part II of THE ENCLOSE Study

In part II of the study, the main aim was to identify the best overall response (BOR) to treatment rate, defined as the proportion of patients with complete response or partial response. The response to treatment rate was evaluated after three and six cycles of chemotherapy and was assessed using radiological imaging such as computer tomography, magnetic resonance imaging or bone scans. The study also evaluated the disease control rate (DCR), defined as the proportion of patients with complete response, partial response, or stable disease. The BOR rates in D2 and D3 groups were 29.63% and 22.41%, respectively. The DCR rates after three cycles in D2 and D3 groups were 87.04% and 82.76%, respectively.



Approximately half of patients with breast cancer in India are diagnosed in the late stages of this disease.

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Through its patented tablet-in-tablet technology, Intas Pharmaceuticals Ltd has developed the first oral fixed-dose combination (FDC) tablet of capecitabine and cyclophosphamide.

PROMISING EFFICACY AND SAFETY OF THE FDC

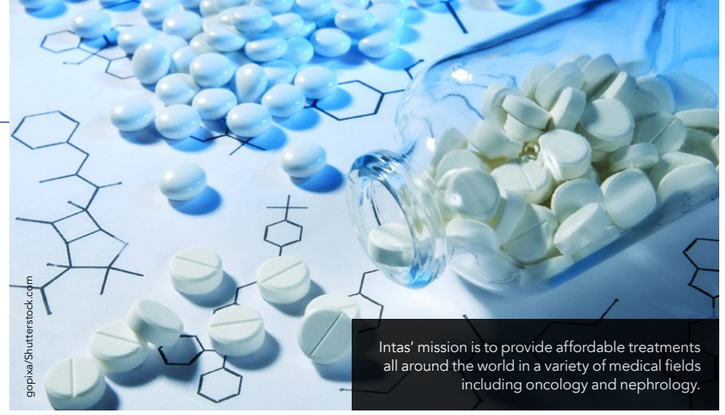
The study highlights that capecitabine and cyclophosphamide combined in one oral tablet is an attractive chemotherapy option that could be preferred by patients, while the reduced pill burden could also improve treatment adherence. Additionally, the FDC's synergistic antitumour effect is thought to add extra value to the treatment, potentially resulting in a reduced dose of capecitabine for MBC disease control, consequently ameliorating the side effects that are often associated with such treatments.

The pharmacokinetic data confirms the hypothesis of the synergistic antitumour effect of the two components of the FDC. When it comes to the drug's safety, it is worth mentioning that the most common side effects were hand–foot syndrome (redness and blisters on the skin of the palms of the hands and the soles of the feet), vomiting, fever, and nausea. The incidence of these side effects was lower compared to previous studies and is thought to be related to the lower doses of these agents used in THE ENCLOSE trial.

ABOUT INTAS PHARMACEUTICALS LTD

Intas Pharmaceuticals Ltd is a leading multinational pharmaceutical company that highly values innovation and

treatment affordability for everyone. The company is present in more than 85 countries worldwide with an extensive range of medications, including 35 oncological drugs available globally and five more under development that will be launched in the market over the next year. The company's innovative approach has led to solutions that have transformed treatment approaches and improved the lives of millions of patients to date. Its progressive future strategy includes expansion of its highly automated facility in India. This modern manufacturing unit can produce more than one billion oral tablets per month as well as five million injectable drugs. With worldwide operations, and a strong pan-European footprint including more than 45 countries, Accord Healthcare (a wholly owned subsidiary of Intas Pharmaceuticals Ltd) develops, manufactures, and distributes affordable medicines, and has one of the most active launch programmes in the European pharmaceutical sector.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Intas' mission is to provide affordable treatments all around the world in a variety of medical fields including oncology, ophthalmology, nephrology, rheumatology, and also hormone-based therapies. To achieve this goal, Intas is currently investing on multiple fronts, such as biosimilar (biologic medical products that are a copy of the original product) development, groundbreaking automation technology and also in attracting talented and ambitious researchers to continue raising the bar of healthcare excellence worldwide.

Q&A

Dr Sudeep Gupta, MD, DM
Director, ACTREC (Advanced Centre for Treatment, Research and Education in Cancer); Professor of Medical Oncology, Tata Memorial Centre, Mumbai, India

How prevalent is breast cancer in India and what do you feel are the main challenges for patients?

As per WHO's Globocan 2020, the number of new breast cancer cases in India was 178,361 while the five-year prevalence was 459,271. In India, patients presenting with breast cancer tend to be premenopausal, with a peak age of diagnosis between 40 and 50 years. This is concerning, as early-onset breast cancer is more aggressive and has a poorer prognosis than if diagnosed later in life. Breast cancer and its treatments have an overwhelmingly adverse impact on patients' physical and mental health, and general quality of life. Breast cancer also carries a significant economic burden for patients' families. The substantial out-of-pocket treatment costs are catastrophic for many patients without healthcare insurance. Associated adverse effects (AEs) and long-term consequences of anticancer treatment are major factors, both for patients and for clinicians. Almost all patients experience at least one AE. The most often observed chemotherapy-related AEs are nausea and vomiting, anaemia, weight loss, and anorexia. With chronic diseases such as cancer, patients face issues with adherence due to fatigue resulting from long-term treatment. In addition to this, patients often need to take multiple drugs for the treatment of MBC as well as for their associated comorbidities, which causes inconvenience and thereby decreases treatment compliance.

What is the current treatment for breast cancer in India?

Chemotherapeutic agents, including anthracyclines and/or taxanes are important components of current treatment; around one-third of the patients eventually have disease progression. Cancer is one of the most complex areas of medicine and it poses a real challenge in India. In particular, breast cancer tends to be diagnosed at a relatively advanced stage, often after it has transformed to a metastatic tumour. Thus, the management of MBC is aimed at symptom palliation and prolongation of overall survival. For a subgroup of patients with MBC without any targetable mutations, conventional chemotherapy drugs continue to be a major component of the treatment regimens.

Can you tell us a bit more about THE ENCLOSE study of the fixed-dose combination (FDC)?

THE ENCLOSE trial is a first-of-its-kind prospective registrational trial to assess this FDC, unlike previous studies which studied capecitabine and cyclophosphamide as separate formulations. I expect this FDC of oral anticancer drugs to be a very convenient and attractive option, both for patients and physicians. Most patients prefer oral treatments to injections, as the tablets can be easily taken at home. It offers patients more freedom and a sense of control over their treatment. It will significantly improve the standard of care for patients. As patients tend to comply better to the regimen with this convenient oral therapy, one can expect improvement in outcomes for these patients. This new combination therapy has the potential to change the landscape for palliative care of the patients with late-stage breast cancer. It provides a convenient administration of both drugs within a single tablet, giving an effective treatment with good acceptability.

This fixed-dose oral combination treatment is a world first for metastatic breast cancer. What difference will this treatment make to your patients?

The fixed-dose combination of capecitabine and cyclophosphamide is effective and well-tolerated in the management of patients with MBC who have been previously treated with anthracycline and/or taxane chemotherapy. It shows a good disease control rate and safety profile. Its reduced pill burden and patients' preference for oral drugs makes this treatment a very attractive option for MBC. I expect it to make a real difference to patients' lives. Moreover, the combination is made available in two strengths (capecitabine 700mg + cyclophosphamide 30mg, and capecitabine 400mg + cyclophosphamide 20mg). This helps in dose titration as per the response or tolerability.

Q&A

Mr Satyavan Dhavale
M Pharma (Bio Pharmaceutics)
Associate Vice President, Formulation Development, Intas Pharmaceuticals Ltd

Can you describe the challenges you faced developing this formulation?

Despite advancements in therapy and awareness initiatives, the challenges linked with breast cancer continue to grow in India. The development of Comcapsy® is a testament to the commitment from Intas towards meeting society's unmet medical needs through research-driven solutions. Developing the fixed-dose combination of capecitabine and cyclophosphamide has been a challenge. A stable pharmaceutical composition was difficult to achieve due to incompatibility between the two therapeutic agents, specifically total impurity levels were found to be increased drastically.

How did Intas overcome challenges in developing the fixed-dose combination?

Intas' success and growth is a direct influence of the company's extensive research and development and manufacturing capabilities. We continually strive to innovate, optimise, and evolve cancer treatments. Every year, Intas invests 6–7% of its revenue in research and development. We operate 15 (formulation, R&D, and distribution) facilities, of which ten are located in India, and the rest in the UK and Mexico. Building on our patented bilayer tablet formulation, we have developed a novel process for the preparation of capecitabine and cyclophosphamide 'tablet-in-tablet'.

What makes this formulation unique compared to other treatments available?

Capecitabine and cyclophosphamide are oral agents with potential synergy. Our unique two-tablet FDC was developed using Intas Pharmaceuticals Ltd's patented 'core tablet-in-tablet formulation' (US patent granted for particle size [US10016447B2] and in process for 'tablet-in-tablet' [US20190142755A1]. This 'tablet-in-tablet' or compression-coated tablet consists of two parts; one is an internal drug core, and another is an external drug shell. The external drug layer mainly surrounds the inner core, and final film coating controls the strength of the product, the release of the drug, and the stability. This world's first fixed-dose combination of capecitabine and cyclophosphamide is a testament to the long-standing commitment from Intas in biopharmaceutical development, research, and manufacturing. Comcapsy® takes advantage of the complementary mechanisms of action for each type of drug and reduces some of the adverse effects observed with the high dose of individual drugs.

What can you comment about the philosophy of Intas Pharmaceuticals Ltd?

Following the success of THE ENCLOSE study, the combination treatment was marketed, post regulatory approval, by the Indian drug regulatory authority in April 2020. Our 'Make It Better' philosophy defines our ambition for this formulation. Intas Pharmaceuticals Ltd will manufacture the FDC in its own state-of-the art production facility.

Behind the Research

Intas Pharmaceuticals Ltd

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Bio
Intas Pharmaceuticals Ltd is one of the leading multinational pharmaceutical formulation, development, manufacturing, and marketing companies in the world. It crossed the $2.3 billion mark last year and is valued at over US $5 billion, with a geographic footprint spanning over 85 countries across the globe. Part of the Intas group, Accord Healthcare Ltd is one of the fastest-growing pharmaceutical and biosimilars companies in Europe, with one of the largest market footprints of any European generic company.

Collaborators
Lambda Therapeutic Research Ltd

Research Objectives

Intas Pharmaceuticals Ltd is committed to fulfilling unmet medical and societal needs through innovation by developing processes and synthesising molecules that are the need of the hour for improving overall patient care.

References

Gupta, S, Biswas, G, Babu, S, et al (2021) Fixed dose combination of capecitabine and cyclophosphamide in metastatic breast cancer: results from THE ENCLOSE phase 2/3 randomized multicenter study. *The Breast*, 60, 147–54. doi.org/10.1016/j.breast.2021.09.012