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Cost Effectiveness of Lapatinib ditosylate for Management of Breast Cancer in India

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ABSTRACT
With patients in India who had nonmetastatic breast cancer, we conducted this study to assess the incremental cost per quality-adjusted life-year gained with adjuvant Lapatinib ditosylate use as compared to chemotherapy alone. Utilising a societal viewpoint and omitting indirect productivity losses, we employed a Markov model to assess the incremental cost of utilising Lapatinib ditosylate (for 1 year) in comparison to chemotherapy alone. QALYs for the conventional treatment arm were calculated after the model was calibrated using survival data from two Indian cancer registries, whereas the HERA study provided estimates for effectiveness. Based on information from Indian cancer registries and real-world use estimates for various treatment modalities, the cost of treatment was approximated. Analyses of probabilistic sensitivity were conducted to assess parameter uncertainty. Using HERA trial calculations, the incremental benefit per patient, incremental cost per QALY gained, and probability of being cost-effective were estimated to be 1.0 QALYs and 2 lakh INR for a year of lapatinib ditosylate treatment. At the present price in India, using lapatinib ditosylate for a year is not cost-effective. The likelihood of 1-year Lapatinib ditosylate use being cost-effective rises to 80% with a 10%–30% price reduction.

I. INTRODUCTION

Cancer is the second leading cause of mortality worldwide. Therefore, cancer is a serious problem affecting the health of all human societies. In women, cancer prevalence is highest in the breast, lung and bronchus, colon and rectum, uterine corpus and thyroid, respectively. Prostate and breast cancer constitute a major portion of cancer in men and women, respectively [1-2]. Cancer occurs by a series of successive mutations in genes so that these mutations change cell functions. Interestingly, environmental chemical substances with carcinogenic properties influence directly or indirectly the cytoplasm and nucleus of cells, and lead to genetic disorders and gene mutations [3-6]. Viruses, bacteria and radiation rays are other carcinogenesis factors, comprising about 7% of all cancers. Cancer disrupts cellular relations and results in the dysfunction of vital genes. This disturbance is affective in the cell cycle, and leads to abnormal proliferation [7-8]. Proto-oncogenes are responsible for cell division and growth under normal condition, but become oncogenes during genetic mutation, which are most dangerous for cell existence [9].

Types of cancer [10]
A) **Carcinoma**: carcinoma begins in the skin or the tissue that covers the surface of internal organs and glands. Carcinomas usually form solid tumors. They are the most common type of cancer. Examples of carcinomas include prostate cancer, **breast cancer**, lung cancer, and colorectal cancer.
B) Sarcomas: Sarcoma begins in the tissues that support and connect the body. A sarcoma can develop in fat, muscles, nerves, tendons, joints, blood vessels, lymph vessels, cartilage, or bone.
C) Leukemias: Leukemia is a cancer of the blood. Leukemia begins when healthy blood cells change and grow uncontrollably. The 4 main types of leukemia are acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, and chronic myeloid leukemia.
D) Lymphomas: Lymphoma is a cancer that begins in the lymphatic system. The lymphatic system is a network of vessels and glands that help fight infection. There are 2 main types of lymphomas: Hodgkin lymphoma and non-Hodgkin lymphoma.
Hallmarks of Cancer Cell
Seven attributes of cancer; 1) Self sufficiency in growth signals, 2) Insensitivity to anti-growth signals, 3) Evading apoptosis, 4) Limitless replicative potential, telomerase and telomeres 5)

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Sustained angiogenesis, 6) Tissue invasion and metastasis, and 7) Genome instability [11].

Breast Cancer

Worldwide, breast cancer is the most common cancer in women, other than nonmelanoma skin cancer [12]. Breast cancer is a disease in which cells in the breast grow out of control. There are different kinds of breast cancer. The kind of breast cancer depends on which cells in the breast turn into cancer. Most breast cancers begin in the ducts or lobules. Breast cancer can spread outside the breast through blood vessels and lymph vessels. When breast cancer spreads to other parts of the body, it is said to have metastasized. The most common kinds of breast cancer are—

Invasive ductal carcinoma. The cancer cells grow outside the ducts into other parts of the breast tissue. Invasive cancer cells can also spread, or metastasize, to other parts of the body.

Invasive lobular carcinoma. Cancer cells spread from the lobules to the breast tissues that are close by. These invasive cancer cells can also spread to other parts of the body.

Two main molecular targets in breast cancer pathogenesis have been identified.

A) One is estrogen receptor alpha (ERα), which is expressed in approximately 70% of invasive breast cancers. ERα is a steroid hormone receptor and a transcription factor that, when activated by estrogen, activates oncogenic growth pathways in breast cancer cells.
B) The second main molecular target is epidermal growth factor 2 (ERBB2, formerly HER2 or HER2/neu), a transmembrane receptor tyrosine kinase in the epidermal growth factor receptor family that is amplified or over expressed in approximately 20% of breast cancers, and is associated with poor prognosis in the absence of systemic therapy.

Prevelance of breast cancer

Breast cancer is the most common malignancy in women around the world. Information on the incidence and mortality of breast cancer is essential for planning health measures. It was estimated that 1,671,149 new cases of breast cancer were identified and 521,907 cases of deaths due to breast cancer occurred in the world in 2012. According to GLOBOCAN, it is the most common cancer in women, accounting for 25.1% of all cancers. Breast cancer incidence in developed countries is higher, while relative mortality is greatest in less developed countries .

In India, although age adjusted incidence rate of breast cancer is lower (25.8 per 100 000) than United Kingdom (95 per 100 000) but mortality is at par (12.7 vs 17.1 per 100 000) with United Kingdom. There is a significant increase in the incidence and cancer- associated morbidity and mortality in Indian subcontinent according to Indian studies. Earlier cervical cancer was most common cancer in Indian woman but now the incidence of breast cancer has surpassed cervical cancer and is leading cause of cancer death, although cervical cancer still remains most common in rural India.

Table 1 Ranking and Rates for Breast Cancer

Breast	Relative Proportion	Rank	Crude rate	Age adjusted rate
Mumbai	28.8	1	33.6	33.6
Bangalore	27.5	1	29.3	34.4
Chennai	30.7	1	40.6	37.9
Thiruvananthapuram	28.5	1	43.9	33.7
Dibrugarh	19	1	12.7	13.9
New Delhi	28.6	1	34.8	41
Barshi Rural	20	2	13.2	12.4

Molecular targets of breast cancer

Breast cancer is a complex, heterogeneous disease classified into hormone-receptor-positive, human epidermal growth factor receptor-2 over expressing (HER2+) and triple-negative breast cancer (TNBC) based on histological features. Several molecular targets are being explored to target TNBC including androgen receptor, epidermal growth factor receptor (EGFR), poly (ADP-ribose) polymerase (PARP), and vascular endothelial growth factor (VEGF). Receptors, protein tyrosine kinases, phosphatases, proteases, PI3K/Akt signalling pathway, microRNAs (miRs) and long noncoding RNAs (lncRNAs) are potential

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therapeutic targets. miR-based therapeutic approaches include inhibition of oncomiRs by antisense oligonucleotides, restoration of tumour suppressors using miR mimics, and chemical modification of miRs.

II. METHODS

Model Overview

For Indian women with HER2-positive breast cancer, a Markov model was created. These were the 5 health states: disease-free state, metastasis, locoregional recurrence (LR), breast cancer-related death, and all cause mortality. In the next year, 10% of people who acquired LR were expected to go back to being healthy. After that, it was impossible to recover from LR and return to a disease-free state. LR to metastatic transition probabilities were three times higher than those from the disease-free condition to metastasis, We simulated the societal costs and effects of administering adjuvant chemotherapy or adjuvant chemotherapy + Lapatinib ditosylate to a group of patients with surgically resected HER2- positive breast cancer at age 50 years. Costs to the health system and out-of-pocket expenses were both calculated. The costs resulting from lost productivity were not factored in. Life-years (LYs) and quality-adjusted life-years (QALYs) gained were used to calculate outcomes.

Intervention and Control

We considered 1 year of Lapatinib ditosylate along with adjuvant chemotherapy as an intervention and adjuvant chemotherapy (comprising anthracycline and taxane-based drugs) as a counterfactual group in the base case analysis. The base case analysis is presented in 2 scenarios. In base case 1, we used the effectiveness evidence from the HERA trial, whereas in base case 2, the effect size of the joint analysis was used; everything else remained constant.

Three alternative intervention scenarios were considered based on the duration of Lapatinib ditosylate use: 1 year, 6 months, and 9 weeks, respectively. Patients in a disease free, LR, or metastatic state were assumed to be managed as per standard international (National Comprehensive Cancer Network) and national (Indian Council of Medical Research) guidelines.

Cost

All patients in the intervention arm's first year were given the option of receiving Lapatinib ditosylate infusions at 8 mg/kg for the first cycle and 6 mg/kg for the following 16 cycles, assuming an average weight of 60 kg. According to the results of earlier studies, the average weight of Indian women with breast cancer was predicted.29,30 The cost of outpatient (OPD) oncology and cardiac consultation, EKG, echocardiography, mammography, and hormone therapy was included for individuals in the intervention arm who had a disease-free health status.

Costs for clinical evaluation (OPD consultation), standard diagnostic testing, and radiologic tests were included for those who had LR. The price of different patient care procedures, such as local mastectomy, radiation, chemotherapy, and hormone therapy, was also factored in. The Indian Council of Medical Research cancer registry's numerous diagnostic procedures and treatment regimens (chemotherapy, radiation, hormone therapy, and surgery) were also considered.

Additionally, the intervention arm's cost for managing cardiac problems was included. The cost of oncology OPD consultations, mammograms, and hormone medication for participants in the control arm of the study was included. A similar set of hematologic, diagnostic, and radiologic testing as well as recurrent breast cancer care recommendations were used for patients with an LR or metastatic health state.

Sensitivity Analysis

Through the use of second-order Monte Carlo simulation, a probabilistic sensitivity analysis was conducted. Transition probability values changed by 10%, but utility and cost values varied by 20% each around the base value. The utility values for the health condition and transition probability were parameterized using the beta distribution. Gamma distribution was applied similarly to cost parameters. There were only 1,000 iterations allowed. In order to compare the cost-effectiveness of 6-month and 9-week Lapatinib ditosylate use to conventional chemotherapy, we performed a subgroup analysis.

The estimations reported in the 2 studies PERSEPHONE and PHARE, respectively, were used to calculate the HRs for DFS and cardiac events with 6 versus 12 months of Lapatinib ditosylate treatment.50,51 The incremental cost-effectiveness ratios (ICERs) were calculated individually using the HR for DFS provided in each trial because the estimations of the 2 studies varied slightly.

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III. RESULTS

One-Year Lapatinib ditosylate : Base Case 1 (Efficacy of the HERA study). Adjuvant Lapatinib ditosylate plus chemotherapy for one year was shown to have a lifetime discounted cost per patient of INR 362,000 similarly, patients receiving adjuvant chemotherapy alone suffered a lifetime cost of INR 120,160. Lapatinib ditosylate use resulted in an increased cost per patient of INR 240,900 Lapatinib ditosylate and chemotherapy administered alone resulted in QALYs lived by each patient of 6.6 and 5.3 years, respectively

One-Year Lapatinib ditosylate : Joint Analysis Effectiveness Base Case 2.

Lapatinib ditosylate had lifetime and incremental expenses of INR 3,37,935 (US$4,833) and INR 2,32,000 per patient, respectively. Lapatinib ditosylate -using patients had LYs and QALYs of 9.0 and 8.0, respectively. 1.88 life-years and 1.79 QALYs gained were shown to be the incremental health benefits per patient. Lapatinib ditosylate would therefore cost more for a 1-year treatment period, costing INR 1,22,000

Subgroup and Sensitivity Analyses

According to effectiveness estimates from the PERSEPHONE and PHARE trials, the incremental cost per QALY gained with 6-month Lapatinib ditosylate use was determined to be INR 111,555 and INR 113,080 . Given the efficacy shown in the Short HER and FinHER trials, the incremental cost of 9-week Lapatinib ditosylate use per QALY gained was calculated to be INR 53,367 and INR 38,300 respectively.

The results of cost effectiveness are largely dependent on the cost of Lapatinib ditosylate , the value of DFS after a year, and the likelihood that a patient receiving chemotherapy will shift from a disease-free to a metastatic state. According to the results of the probabilistic sensitivity analysis, there is a 4% chance that 1-year Lapatinib ditosylate use will be financially advantageous at a willingness-to-pay threshold equal to per capita GDP.

Overall, our results show that Lapatinib ditosylate treatment for a year is not financially advantageous at the current cost. However, a 15% to 35% price cut would make using Lapatinib ditosylate for a year cost-effective. It is economical to use Lapatinib ditosylate for both 6 months and 9 weeks. However, 9 weeks of Lapatinib ditosylate use has a smaller incremental cost and is therefore the most effective choice, even though the number of QALYs gained is statistically comparable. Utilising effectiveness data from numerous trials, we have presented our findings.

Second, rather than assuming a constant HR, as most past economic evaluations have done, we used estimates of HRs as reported at various time points (as in the HERA experiment). Third, we adjusted our model based on breast cancer survival from 2 Indian cancer registries to forecast survival in the counterfactual scenario..

Our results are therefore considerably more applicable and typical of the Indian population. Our parameter values for the cost of managing breast cancer and its complications were derived from regionally available cost studies32,33 or provider reimbursement rates under one of India's largest social insurance schemes.34,58 Similarly, an investigation of hospital-based cancer registries was used to determine the patterns of therapeutic utilisation particular to each stage of the disease..31

Our cost analysis is reasonable from a national perspective as a result. In various studies, the incremental gain in LYs has ranged from 0.6 to 2.87, and the incremental gain in QALYs has ranged from 0.49 to 2.83.11-14,16-19,21,25,26,36-42,59 Lapatinib ditosylate treatment resulted in an incremental health benefit that was 1.48 LYs and 1.29 QALYs, both of which are well within the published evidence's acceptable range. The additional price per QALY acquired when it comes to purchasing

IV. CONCLUSION

According to the results of our investigation, Lapatinib ditosylate use for a single year is either not cost-effective or has a high degree of cost unpredictability. The cost-effectiveness of 1-year Lapatinib ditosylate use would be achieved by reducing the drug's price by 35%. The most effective course of action in the current situation is to take Lapatinib ditosylate for nine weeks. It is necessary to update the clinical recommendations and provider compensation for cancer treatment under health insurance programmes.

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