Comparing Tyrosine Kinase Lapatinib Nano-Therapy Interventions to Trastuzumab Chemotherapy: Which is Most Effective for U.S. Females with HER2-Positive Breast Cancer?

Victoria Rodriguez Silva

Stony Brook University School of Health Technology and Management

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***Introduction***

Invasive breast cancer is a common diagnosis for women to receive in the United States. According to estimations provided by the American Cancer Society, about 1 in 8 women will be diagnosed with some form of invasive breast cancer in their life. 1 HER2-positive breast cancer is a subtype characterized by the breast tumor of a patient carrying a large amount of the growth factor HER2 protein on the outside of the breast cells. 2 HER2-positive breast cancer typically grows and spreads at a faster rate in comparison to other forms of breast cancer.2 This research study is comparing the traditional trastuzumab chemotherapy and the new developmental tyrosine kinase lapatinib nano therapy treatment options for HER2-positive breast cancer to identify which one is most effective in treating females in the United States aged 30-65 years old. This was the selected age group because data shows that HER2- positive breast cancer has a high diagnosis and incident rate in adults below the age of 65, and about 44% of these diagnostic rates correlate to women within the 30-49 age range. 3 Breast cancer classified as HER2-positive is highly aggressive, invasive and account for approximately 20% of all breast cancer cases. 4 It has been discovered that treatment options specifically targeting the HER2 protein are highly effective but that current chemotherapy methods and drugs lack the ability to target the growth factor causing issues. 5 For these reasons a side-by-side comparison of traditional chemotherapy to a cancer nano therapy treatment option would be vital to help these women get the targeted defense they need at a critical time in their cancer diagnosis.

Throughout the years, much about HER2-positive breast cancer and its treatment options has been discovered. This cancer subtype arises from the HER2 gene, which is an acronym for “human epidermal growth factor receptor 2”, that creates proteins which serve as receptors on affected breast cells. 6 In a normal microenvironment, HER2 receptors help with healthy breast cell growth but in approximately 10-20% of breast cancers this function goes awry and instead created excess copies of the HER2 gene. 6 These additional amounts of the HER2 gene contribute to the generation of too many HER2 receptors which is what causes breast cells to grow and divide with no control. 6  Currently, the trastuzumab antibody and its role in chemotherapy has had major impact on HER2-positive breast cancer treatment. Adding trastuzumab to traditional chemotherapy has been proven to “reduce the risk of recurrence by approximately 40% and the risk of death up to 34%” in clinical trials. 7 It has also been observed that trastuzumab combined with standard chemotherapy enhances the “pathologic complete response”, which is the absence of residuals derived from invasive or in-situ breast cancer identified using a complete evaluation of breast tissue and any surrounding lymph nodes after treatment. 8 However, there is new documentation noting that patients who have undergone trastuzumab chemotherapy have built resistance to the drug. 9 Therefore, an alternative treatment for HER-2 positive breast cancer must be considered and studied further.

Nanomedicine, specifically cancer nano therapy, has shown much potential in effectively targeting cancer sites and directly delivering cancer drugs to affected cells. Nanoparticles utilized in developing nano therapy interventions are able to bind to cancer cells directly due to their unique properties which deliver chemotherapeutic drugs effectively to the source of the amplification site. 10 It has been proposed that nanotechnology can eliminate issues associated with traditional breast cancer treatment such as “the lack of early detection, inadequate drug concentrations, and the inability to monitor therapeutic responses” 11. Tyrosine kinase lapatinib nano therapy is an oral inhibitor that has the potential to treat HER2-positive breast cancer because of its ability to inhibit HER2 amplification. 7 This inhibition is possible because of lapatinib’s chemical composition which enables inhibitors to block phosphorylation of the growth factor receptors reversibly. 12 Currently, Lapatinib is applied after a patient has undergone the trastuzumab cancer treatment, but it has been considered superior because of its contribution to stalling the impact of receptors and cell expansion before the breast cancer spreads throughout the body. 13 Although cancer nano therapies are still being developed and studied, the need for solutions in regards to HER2-positive breast cancer is essential now more than ever because of the resistance and reoccurrence of this disease that many women are experiencing after being treated with the trastuzumab option.

The current gaps or limitations with cancer nano therapy options pertain to safety and costs. Nanomedicine is a new science that arose in the early 20th century and it is still in its developmental stages. 14 For this reason, there must be further toxicology and safety-related assessments conducted before it is able to be distributed to the general population, or in this case for use in a research study.15 Another primary issue with nanotechnologies is the rapid growth of the field in such a short amount of time, with the lack of concrete documentation and trial results to help identify the risks and management of these revolutionary concepts.15  Furthermore, the costs for cancer nano therapy interventions are extremely high and not readily accessible.11 The use of tyrosine kinase lapatinib nano therapy could be a solution for women with HER2-positive breast cancer, but the limitations mentioned above make this a difficult goal to reach.

Referencing the information provided on what is known about the two treatment options, this research study will aim to answer the question of whether tyrosine kinase lapatinib nano therapy or traditional trastuzumab chemotherapy are more effective in treating women in the United States aged 30-65, who have received a HER2-positive cancer diagnosis within a 30–60-day time period. It is hypothesized that amid a side-by-side comparison the lapatinib cancer nano therapy intervention will prove itself to be more effective in treating women with HER2-positive breast cancer because of the drug resistance seen in trastuzumab paired with chemotherapy today.

***Methods- Study Design***

This research study will use a prospective crossover study design in order to compare the effects of tyrosine kinase lapatinib nano therapy and traditional trastuzumab chemotherapy treatment for patients with HER2-positive breast cancer. Crossover studies consist of participants being randomly assigned into two groups where each group undergoes the same two treatment options at different time intervals for direct comparison.16,17,18 In this study, the participant will serve as their own control variable to compare the outcomes of both cancer treatment options.16 In this study, the participants will be initially receiving either the lipid nano therapy intervention or trastuzumab chemotherapy for the first 3-month long session. Afterwards, a “washout period” will take place where participants will not be receiving either of the treatment options for a two- week period.16 After this period, the two groups will switch and undergo the other treatment option for another 3-month long session. This study is considered a prospective study because the participants would not have had previous exposure to any form of cancer treatment, except for their initial surgery. This study will also be a closed study because all participants will remain the same until the end of the study. Figure 1 provides an outline for the timeline of the research study, including the durations and descriptions of each session of the study.

Research Study Timeline

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| --- | --- |
| **Introduction**  **(2 Meetings at the beginning and end of the opening week, e.g. Monday and Friday of same week)** | Selected participants are randomly assigned to Group A or Group B, described the conditions and protocols for the research study, and provided information on both treatment types to independently go over and read thoroughly. Questions or concerns can be discussed in scheduled joint meetings. |
| **First Session**  **(First 3 months of treatment)** | Group A is given traditional trastuzumab chemotherapy and Group B is given the tyrosine kinase lapatinib nano therapy for HER2 breast cancer for a 3- month long period. |
| **“Washout Period”**  **(2 weeks of no treatment)** | During this period, both groups will not undergo any form of treatment for 2 weeks. Participants will be interviewed to see how they are feeling after the first session and data will be collected. |
| **Second Session**  **(Second 3 months of treatment)** | For the second session, Group A and Group B will switch treatment options for the next 3-month long period. |
| **Conclusion**  **(2-3 weeks to conduct interviews, analyze results, and draw up conclusions)** | After the second session, the research study will end. Participants will be interviewed once more and results will be analyzed. Participants will then have the option to continue with the most effective treatment option, if they wish. |

***Methods- Setting***

This research study is going to take place at the Baylor College of Medicine Lester and Sue Smith Breast Center in Houston, TX for all of the sessions enlisted above.19 During the individual sessions, the participants will stay in the center as admitted patients for the Baylor medicine hospital system.

***Methods- Participants***

The recruitment process for this research study will primarily focus on gathering female patients that have recently been diagnosed with HER-2 positive breast cancer in Houston, Texas. Online postings via social media platforms, digital and physical newspaper articles, as well as potential partnerships with nearby centers or hospitals providing breast cancer treatment will assist in gathering the desired population for this study. Those interested have the opportunity to contact a hotline provided in the social media advertisements and newspaper articles for the study, and after expressing interest will be advised to provide an email or phone number to discuss further steps. A link to create an appointment for a consultation with our research team’s providers will be sent to those who provided an email or a representative will contact those who provided a phone number to set up a consultation. After participants of interest have been seen by our provider and the variables needed for the study have been met, those selected will be contacted and given information to attend the introductory session of the study. The total number of participants desired for this study is 12, for an equal distribution between the two sessions and for smoother follow ups thereafter.

The inclusion criteria for this study consists of female participants within the 30-65 age range living in Houston, TX who have been diagnosed with HER2-positive breast cancer no later than 60 days before the commencement date for the study, along with the participants being willing to stay within the Baylor College of Medicine’s center for the entire duration of the research study. The exclusion criteria for this study consists of non-female participants, females above or below the selected age range, participants living outside of the state of Texas, participants who have either had a type of breast cancer or have received some form of breast cancer treatment in the past, and any participants who smoke or drink on a regular basis.

***Methods: Variables***

Progress during both treatment sessions will be monitored using imaging techniques and endoscopes to determine if detected tumor(s) or clusters of cancer cells are getting bigger, smaller, or staying the same size. More specifically, CT scans will be used to analyze the size and shape of the HER2 tumor(s) every 3 weeks throughout both sessions.20 PET scans will also be used to identify the presence of HER2 protein or receptors every 4 weeks throughout both sessions.20 These imaging times are spaced out to avoid an addition excess of radiation for participants.

The participants would need to have been recently diagnosed with HER2-positive breast cancer for the study, or have undergone initial surgery if needed, no later than 60 days before the study for the most optimal treatment period and analysis for the disease. Data suggests that the sooner a patient undergoes chemotherapy or cancer treatment after diagnosis or initial surgery, the better the outcome of the treatment.21 This is important for this study because comparing the two treatment options during the optimal time for a patient to improve in response to treatment would provide insightful data and results.

The stage of HER2- positive breast cancer or the size(s) of the tumors have not been identified because the participants will be their own controls. In other words, the selection process only includes females with HER2- positive breast cancer but does not specify the stage or size because this study is simply trying to determine which treatment option is better. Variety in regards to stages or sizes of tumors could potentially provide more insight into the treatment options by studying progress along multiple scopes or types of HER2 cases.

***Methods: Data Sources and Measurement***

As previously mentioned, imaging techniques (CT scans, PET scans, and endoscopes) will be used to track the progress of both treatment options for all participants during the two 3 month-long sessions. CT scans and PET scans will be conducted every 3-4 weeks (on separate days) to monitor if the tumor has grown larger, smaller, or stayed the same size.20 The dimensions of the tumors or cancer cell clusters (depending on stage) will be notated along with any distinguishing characteristics observed in either scans. At the end of each session, participants will comment on how they are feeling physically and data collected over the 3-month period will be analyzed for patterns or trends throughout the course of each treatment type.

There has been evidence to suggest that delaying breast cancer treatment for too long leads to an increase in risks, spread of the disease, and decreases the patient’s chance of survival.21 According to a population-based study conducted under JAMA Oncology, the majority of invasive breast cancer patients ranging from stage 1 to stage 3 started chemotherapy within 31-60 days after surgery, with the average time to chemotherapy being 46 days.21 No evidence of adverse outcomes was documented during the 31–60-day time frame but it was established that patients treated 91+ days had lower survival rates.21 Hence, this study will conduct two treatment options no later than 60 days to eliminate adverse outcomes as much as possible.

In this study, the participants will be their own controls when comparing the two treatment options. However for better guidance the stages must be identified during each participant’s initial consultation. Traditionally, stages were determined by the following criteria: size of the tumor, if the tumor has grown within tissue, the appearance of lymph nodes or lack thereof, and if the disease has spread to other areas besides the breast. However, recent changes have added the question of how much of the HER2 protein cells are being replicated when clarifying the stage of HER2-positive breast cancer. Using information from BreastCancer.org22, Figure 2 provides an easy-to-follow description of the breast cancer stages:

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| --- | --- |
| **Stage 0** | * Non-invasive * No evidence of cancer cells * Non-cancerous abnormal cells |
| **Stage 1A** | * Invasive * Tumor measures ~2cm * Cancer has not spread to areas besides the breast * No lymph nodes detected * Estrogen-receptor positive classified as this stage |
| **Stage 1B** | * Invasive   **Either:**  -No detected tumor in the breast but small groups of cancer cells >.2mm but also <2mm detected in lymph nodes  -Tumor in the breast <2cm and small groups of cancer cells >.2mm but <2mm   * **HER2 positive cancer** with a tumor between 2cm-5cm, found in 1-3 lymph nodes, and estrogen-receptor positive classified as this stage * **HER2 positive cancer** with a tumor more than 5cm across, found in 4-9 lymph nodes, “grade 2” and estrogen-receptor positive classified as this stage |
| **Stage 2A** | * Invasive   **Either:**  -No tumor in the breast but cancer detected in 1-3 lymph nodes or in lymph nodes near the breast bone  -Detected tumor measures ~2cm or less and has spread to lymph nodes  -Tumor is >2cm but <5cm and has not spread to lymph nodes   * **HER2 positive cancer** with a tumor more than 5cm across, found in 4-9 lymph nodes, “grade 3” and estrogen-receptor positive classified as this stage |
| **Stage 2B** | * Invasive * Inflammatory characteristics   **Either:**  -Tumor is >2cm but <5cm and smaller groups of cancer cells >.2mm but <2mm are in lymph nodes  -Tumor is >2cm but <5cm and cancer has spread to 1-3 lymph nodes or to lymph nodes near breast bone  -Tumor is >5cm but has not spread to any lymph nodes |
| **Stage 3A**  **Stage 3A (cont.)** | * Invasive   **Either:**  -No tumor found or tumor of any size detected with cancer cells in 4-9 lymph nodes or in lymph nodes near the breast bone  -Tumor >5cm or small groups of cancer cells >.2mm but <2mm found in lymph nodes  -Tumor >5cm and cancer has spread to 1-3 lymph nodes or lymph nodes near the breast bone   * **HER2 positive cancer** tumor of any size that has spread to more than 10 lymph nodes or lymph nodes near the collarbone or breastbone and estrogen-receptor positive classified at this stage |
| **Stage 3B** | * Invasive * Inflammatory breast cancer   **Either:**  -Tumor can be any size but has spread to the chest wall, breast skin and caused swelling or an ulcer  -Cancer spread to 9 lymph nodes or lymph nodes near the breast bone |
| **Stage 3C** | * Invasive   **Either:**  -May be no sign of cancer in the breast area  If a tumor is present, it can be any size and has spread to the chest wall, breast skin and has spread to 10+ lymph nodes  -Cancer has spread to lymph nodes above or below the collarbone  -Cancer has spread to lymph nodes near the breast bone |
| **Stage 4** | * Invasive * Metastatic * Breast cancer has spread beyond the breast and associated lymph nodes to other organs |

***Methods- Bias***

There could potentially be selection bias during the recruitment process since not all have access to social media platforms or mobile devices to email or contact a representative to express interest in the study. In this regard, technology illiteracy and broadband access could be another imbedded issue. Additionally, the recruitment process included possibly reaching out through partnerships with breast cancer treatment centers, which could also lead to bias depending on the demographic group(s) looking into treatment options in these centers.

***Methods- Study Size***

The recruitment process will terminate after 12 female participants within the age range of 30-65 with HER2- positive breast cancer living in Houston, TX have been identified. The maximum amount of participants in each of the randomly assigned groups will be 6. The combined two groups of 12 participants will be housed in the single floor of Baylor College of Medicine Lester and Sue Smith Breast Center dedicated to clinical trials.

***Results- Based on Jupyter Notebook Dataset***

The dataset entitled, “COVID-19 Estimated Patient Impact and Hospital Capacity by State”, was used for further analysis in a Google Collab Jupyter Notebook. The data was created in December 2020 by the U.S. Department of Health and Human Services to reflect three values pertaining to capacity for each state.23 These three values include: (1) the number of total inpatient beds occupied by each state at a given time, (2) the number of inpatient beds being occupied by COVID-19 patients by each state at a given time, (3) the number of ICU beds occupied by each state at a given time. The number of total inpatient beds for each state was represented by the column entitled “inpatient\_beds\_occupied”.23 The number of inpatient beds occupied by COVID-19 patients was represented by the column entitled “inpatient\_beds\_occupied\_by”.23 The number of ICU beds occupied for each state was represented by the column entitled “staffed\_adult\_icu\_beds”.23 The dataset also created subcategories for additional information pertaining to these three core variables, such as percentage values as well as the minimum and maximum amounts for each of the three values. The purpose of this dataset was to analyze and show the impact these three categories had on a selective number of states.

After the needed packages and dataset were uploaded into the Google collab Jupyter Notebook, the independent and dependent variables of interest were identified. The notebook focused heavily on the three core values (Inpatient beds, COVID-19 patients, and ICU beds) and the states column to generate conclusions for the dataset. After the variables were identified, the columns containing missing values were addressed. The “state” column had generated a mysterious acronym “CW”, which is not representative of any U.S. state so this was deleted from the dataset to avoid skewed results during the analysis. After this transformation of the entire dataset to reflect no missing values, transformations were created to group values within the columns. The quartile ranges for the dependent variables (Inpatient beds, COVID-19 patients, and ICU beds) were used to categorize the numerical values as having small, medium or large values. This function provided for easy compartmentalization to see which states had larger values for each of the affected areas.

Since categories were enabled for the numerical values of the three core columns, the issue of states being “stacked” or appearing more than once in the dataset’s rows had to be addressed. As previously mentioned, a function was performed to eliminate a mysterious value the dataset had placed under the “states” columns called “CW”, so all that needed to be done was to group states by their acronyms and combine the values for each state using a mean function. This newly generated dataset allowed for cleaner visualization and easy analysis of the information being represented. Three bar graphs were created to show the relationship between total inpatient beds, inpatient beds being used for COVID-19 patients, and the total number of ICU beds occupied for each state. An additional pie graph was created to show the percentages of values that each state shared within the dataset. These are the conclusions based on these visualizations.

In the graph showing the relationship between the total number of inpatient beds occupied for each state, the states with the highest occupancy included California, Florida, and New York. This means that these three states had the highest amounts of inpatient beds in use for the time periods that this data was collected. In the graph showing the relationship between the total number of inpatient beds occupied by COVID-19 patients for each state, the states with the highest occupancy levels included California, Illinois, Michigan, and Pennsylvania. According to the dataset, these four states had the highest impact pertaining to both COVID-19 and hospital occupancy. In the graph showing the relationship between the total number of ICU beds occupied for each state, the states with the highest occupancy included California, Florida, and New York. This means that these three states had the highest use for ICU beds and hospital capacity impact during the collection of this data. Conclusively, California was the state who had experienced the most impact for all three categories.

***Conclusion***

Both of these assignments helped me realize how much goes in to creating a research study and the extent organizations have to go to create a meta-dataset for public use. For the research question and research method portion, I would have never taken the time to acknowledge all of the different variables and steps needed to make an effective research study if it were not for this assignment. There were small variables that one would think did not matter but actually make a huge difference in the entire process, such as the recruitment process for finding participants for a study. For the coding and data analysis portion of this assignment, the exposure to different value types and how information is represented was nothing that I had any knowledge of before this session’s instruction. Overall, I realized how much goes in to planning a research study, the significance of knowing what the variables amid the study will be and how they are to be dealt with, and stepped into the world of getting familiar with taking a dataset and analyzing it to make conclusions.

If I had the expertise and time, I would have liked to dive into the collection date and geocoded state columns. It would have been interesting to see if the time of year affected the amount of impact for the different sectors of occupancy that the dataset was covering, For example, were the number of inpatient beds occupied by COVID-19 patients per state higher in the spring than in the fall? By looking at the collection dates, questions such as these could be answered. Additionally, exploring the geocoded states columns could have been fun and used to create map images for the different occupancy sectors in each state. This could have answered the question of which regions in each state had the highest impact versus just comparing entire states to each other. These were two columns that I was intrigued in further analyzing but could not figure out the coding side of making them work.

According to the dataset, California was the state who suffered from the most hospital capacity impact for the number of inpatient beds occupied in general, for COVID-19 patients, and for the total number of ICU beds being occupied for the entire time period that this data was being collected. For this reason, I would strongly suggest political reform and action in providing the state of California with more resources and space for all of the patients that are occupying their facilities. Providers, nurses, and other healthcare workers should also be taken into account. These large amounts of patients, including the cases of COVID-19 seen for California in 2020, could easily lead to physician burnout and shortages of staff members. All in all, California needs better support, resources, and guidance in navigating the influx of people utilizing medical resources.

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