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FACTORS AFFECTING THE OUTCOME OF THE OPERABLE SUBTYPE LUMINAL B BREAST CANCER TREATMENT

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ABSTRACT

Breast cancer is a condition of uncontrolled breast cell proliferation that most frequently develops from the ductal epithelial cells (85%) or lobules (15%) of the breast glands. Poor prognoses for patients can result from cancer's extensive organ metastasis, now the second largest cause of cancer death in women. This study aims to identify the variables that affect how well patients with the operable breast cancer subtype Luminal B respond to treatment at RSUP DR M Djamil Padang. This research used a cross-sectional methodology with a retrospective study approach to identify characteristics that affect the treatment outcome for operable breast cancer subtype luminal B at RSUP DR. M. Djamil Padang. From August to November 2022, the study was carried out in the Oncology Surgery Division of RSUP DR. M. Djamil Padang. With HER2 being the main component, multivariate analysis revealed that HER2 and the kind of therapy were significantly connected with the treatment outcome for cancer patients.

INTRODUCTION

Breast cancer is an out-of-control breast cell growth disorder commonly arising from ductal epithelial cells (85%) or lobules (15%) of the breast glands. The wide spread of cancer to various organs can lead to a poor patient prognosis and become the second leading cause of death from cancer in women. Breast cancer incidence is reported worldwide (Center for Disease Control and Prevention, 2019).

According to the International Agency for Research On Cancer (IARC), in 2012, the incidence of breast cancer ranged to 43.1 per 100,000 women, with a mortality rate of about 12.9%. Report to the Data and Information Center of the Ministry of Health of the Republic of Indonesia, the percentage of breast cancer incidence in women shows the first order with 34.30% of cases, followed by cervical cancer at 19.12%. In Indonesia, the number of new cases of (Pangribowo, 2019) breast cancer was 65,850, with the number of deaths of 22,430 cases in 2020, which increased cases from the previous two years around 58,256 cases in 1 year(Ministry of Health of the Republic of Indonesia, 2016; Rahmatya et al., 2015).

West Sumatra Province is known to have data on breast cancer cases which ranks third most in Indonesia. At RSUP Dr. M Djamil Padang, breast cancer cases were found to increase every year. In 2017 there were 246 cases. In 2018, there were 386 cases; in 2019, there were 421 cases. It resulted in West Sumatra Province being in third place with the highest prevalence of breast cancer in Indonesia after Yogyakarta and East Kalimantan.(Indonesia's Ministry of Health, 2012; Kementrian Kesehatan RI, 2016; Rahmatya et al., 2015).

Molecularly, breast cancer can be divided into three large classes: luminal tumors, over-expression HER2, and Triple Negative Breast Cancer (TNBC) tumors. The division was grouped

based on the expression of immunohistochemistry biomarkers in the form of ER (Estrogen Receptor), PR (Progesterone Receptor), HER2 (Human Epidermal Growth Factor 2), and Ki67. The expressed hormone receptors are associated with breast cancer carcinogenesis and affect the severity and prognosis in breast cancer patients (Dai et al., 2015; Kondov et al., 2018).

Luminal B breast cancer is characterized by Estrogen Receptor positive and/or Progesterone positive, Human Epidermal Growth Factor Receptor 2 negative, and Ki-67>20% or Estrogen Receptor positive and/or Progesterone positive, Human Epidermal Growth Factor Receptor 2 positive. Over Expression Ki67 shows high proliferation activity in cancer cells, so it is associated with a poor prognosis. Luminal B breast cancer is known to have aggressive clinical behavior and has a prognosis similar to non-luminal cancer (including HER2-enriched and basal-like subtypes). Although Luminal B has a high sensitivity to chemotherapy responses, the survival rate of Luminal B breast cancer patients is very low. The study by Li found among 258 cases of luminal B breast cancer, 42 patients had local recurrences, 43 cases had regional relapses, 60 cases had bone metastases and 123 cases had metastases to other places or multiple organ metastases (Li et al., 2016; Mohammed, 2021; Pellegrino et al., 2021).

In addition to poor outcomes, according to the 2013 St. Gallen Consensus, luminal subtype B accounts for nearly 40% of all breast cancers. Research by Mohammed also found breast cancer Luminal subtype B makes up the majority of patients (66.33%) and type A is the rest. Another study by Serrano-Gomez(2021) et al. also got luminal (Serrano-Gomez et al., 2016) subtype B making up the majority of breast cancer types which were 37.2% followed by luminal A (26.2%), triple negative non-basal (NBTN, 11.6%), basal like (9%) and HER2-enriched (8.6%) (Kondov et al., 2018; Li et al., 2016).

Research on breast cancer subtype Luminal B has previously been conducted by Paramita et al in East Kalimantan, Indonesia. The study found that breast cancer of luminal subtype B was found to be the most common intrinsic molecular subtype of breast carcinoma (42.39%). In this study also found Luminal B is the most common subtype in patients aged 35 years, such results suggest younger patients generally have the worst prognosis .(Pellegrino et al., 2021)

Early stage breast cancer which includes stage 0, I, IIa, IIb, is a breast cancer that is still operable and can be treated with advanced chemotherapy, as well as with advanced localized breast cancer, namely stage IIIa, IIIb. Where the clinical outcomes of management in breast cancer are Disease free survival (DFS) and overall survival (OS) and relapse rates in patients. In early-stage breast cancer patients, DFS or disease-free survival increases, the risk of relapse decreases and mortality or OS decreases (Li et al., 2016; Serrano-Gomez et al., 2016).

In a study conducted by Reihan et al who looked at the relationship of malignancy degrees with the Luminal B molecular subtype in breast cancer patients in 2014-2016 at RSUP Mohammad Hoesin Palembang found that luminal subtype B with garde III was found more, namely around 63.7%, while in grade II and grade I it was found as much as 31.7% and 4.6% (Paramita et al., 2019). Determination of hormonal expression in cancer tissues such as estrogen receptors, progesterone receptors, new status of HER-2, as well as the degree of expression of biomarkers Ki67 greatly influences the selection of treatment modalities and can predict outcomes. Estrogen

and progesterone receptors (ER and PR) and HER2 have been shown to have an important influence on breast cancer management. In addition, it has been shown that ki67 has a great impact on the biological activity of the tumor and has a great impact on the prognosis .(Li et al., 2016; Mohammed, 2021; Serrano-Gomez et al., 2016)

Luminal A breast cancer is known to have better outcomes and is more responsive to hormonal therapy, while luminal subtype B is found to have a higher risk of relapse. Therefore, in the Luminal B subtype is also carried out the administration of other therapies such as anti-HER2 (Trastuzumab) and adjuvant chemotherapy .(Chen et al., 2022; Paramita et al., 2019)

Research by Cheang et al. (2009) obtaining that luminal B tumors with HER2- positive were significantly associated with younger age at diagnosis, higher tumor staging, larger tumor size, positive lymph node involvement, and lymphovascular invasion and in regression assays of luminal subtype B were associated with statistically worse recurrence-free survival as well as worse breast cancer-specific survival than luminal subtype A .(Ho et al., 2020)

About 10-34% of breast cancers experience overexpression of HER2 receptors otherwise known as HER2 (+), overexpression of HER2 is associated with amplification of the HER2 gene. In cells undergoing HER2 amplification, there are 500,000-2,000,000 receptors per tumor cell. In addition, HER2 is also known to have no activation ligands, HER2 can act as a form of dimerization with other HER2 proteins, after activation of the tyrosine kinase domain, it can activate the signal of the pathway for breast cancer to occur, so the theory is associated with a poor prognosis and short survival in breast cancer subtype luminal B (Cheang et al., 2009; Ho et al., 2020).

Other studies were also conducted by Kim KH regarding factors affecting treatment outcomes in patients where tumor staging, axillary lymph node status, and Ki-67 expression are prognostic factors of RFS and OS in luminal subtype breast cancer with pathological staging are significant factors affecting RFS in multivariate analysis (Kim et al., 2013).

On the research conducted Zuo et al. In 2017, it was found that the overall *survival* value of 5 years for patients with breast cancer subtype luminal B was 88.4%, which is lower than breast cancer subtype luminal A by 92.6%. In addition, the behavior of breast cancer subtype luminal B is known to be very aggressive due to the amplification of the HER2 gene so that it can affect the overall survival rate of breast cancer patients (Lakhani et al., 2002).

Because breast cancer subtype luminal B is the most common subtype, clinical appearance is more aggressive, often found in young patients, has a worse outcome, has a high risk of recurrence and has a short survival rate compared to other luminal subtypes, and there is still little research on luminal B breast cancer, researchers are interested in analyzing the factors that influence outcomes in the treatment of operable breast cancer. Luminal B subtype at RSUP DR M Djamil Padang. This study aims to determine the factors that influence the outcome in the treatment of operable breast cancer subtype Luminal B at RSUP DR M Djamil Padang.

METHOD

This research is an analytical study using the cross sectional method with a retrospective study approach to determine factors related to the outcome of treatment of operable breast cancer subtype luminal B at RSUP DR. M. Djamil Padang. The research was conducted at the Oncology Surgery Division of RSUP DR. M. Djamil Padang from August to November 2022.

The population in this study was all patients diagnosed with operable breast cancer subtype luminal B who had been diagnosed with breast cancer subtype mluminal B and continued surgical therapy and treatment at RSUP Dr. M. Djamil Padang during the period January 2016-December 2021. The sampling technique in this study used non-probability sampling with the consecutive sampling method. The minimum sample size of the study is determined using the formula:

$$n = \frac{(Z_{1-a/}2)^2 . p . q.N)}{d^2 (N-1) + (Z_{1-a/}2)2 . p . q}$$

Information:

n = number of samples

Z = degree of meaningfulness 95% (a= 0.05) so that the value Z = 1.96 is obtained

P = proportion of population (0.5)

q = (1-p) → 0,5

N= total population of luminal KPD B → 150 people

d = alpha (0.1) or sampling error 10%

$$n = \frac{(1.96)^2(0.5)\ (0.5)(150)}{(0.1)^2\ (150-1) + (1.96)^2(0.5)\ (0.5)}$$

$$n = \frac{(3.84)\ .\ (0,25).\ (150)}{1,49 + 0,96}$$

$$n = \frac{144}{2,45}$$

n= 58.7

n = 59

Based on calculations using the formula above, the minimum sample required in this study was 59 samples to achieve a confidence level of 95%.

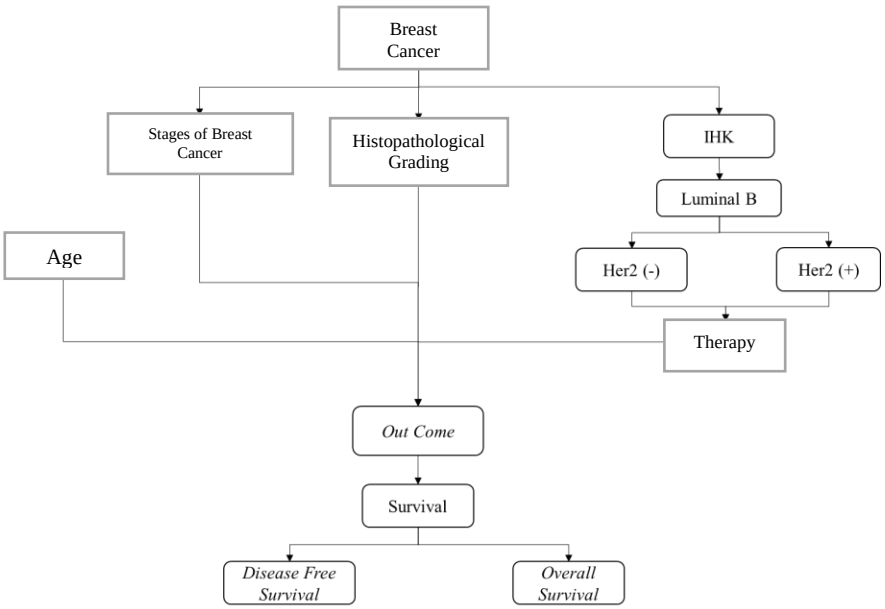

Figure 11. Research Flow

The data obtained from the medical records is collected, then the data processing is carried out manually and continued with a computer program. As for the analysis, researchers used univarate, bivariate, and multivariate analysis.

RESULT AND DISCUSSION

Analysis of the Relationship of Age to Breast Cancer Treatment Outcomes of Luminal Subtype B at RSUP DR. M. Djamil Padang

In this study, it was found that breast cancer patients of luminal B subtype died the most at the age of ≥40 years, but from the results of statistical analysis, there was no meaningful relationship between age and treatment outcomes with a p value of > 0.05, which was 0.368. This is in accordance with a study by Liu et al in 2018 that found no age relationship with the *outcome* of treatment for luminal subtype cancer B. In the study by Liu it was stated that the proportion of younger age patients died more which is different from this study where more patients died at an older age (Liu et al., 2018).

In this study, because more patients have the age of over 40 years, this will indirectly increase the possibility of more patients dying at this age. In addition, the immune system of patients at the age of >40 years is also worse than that of younger ages, so this is the reason why more proportions of patients over 40 years old die. However, the theory of a higher cancer-specific mortality rate at a young age is also acceptable because cancers that appear at a younger age tend to be more malignant and have more aggressive biological properties as stated by Liu et al. (2018). This is the basis for why age does not significantly affect treatment outcomes because there are many other factors that can cause varying outcomes in breast cancer patient outcomes.

In this study, the mean disease free survival of patients aged <40 years was 51.53 months and patients aged ≥40 years was 44.24 months but this difference was not statistically significant. A different thing was found by Lian et al in 2017 where patients aged ≤40 years were significantly related to DFS 5 years which was worse but in the study it was excluded for Luminal B (HER2+) whereas in this study most patients had HER2 + expression so this is likely to cause differences in outcomes. This means that in Luminal B patients who mostly have HER2 + expression, both young and old age have similar recurrence rates and may be more influenced by other prognostic factors (Lian et al., 2017).

In this study, the overall survival mean of patients aged <40 years was 37.47 months and patients ≥40 years was 40.36 months but this difference was not statistically significant. Tang et al found something similar but with statistically significant differences where it was stated that patients under the age of 40 were 2.5 times more at risk of having a bad OS than those over 40 years of age. Short overall survival may be associated with the biological nature of tumors found to be more aggressive at the age of under 40 years (Tang et al., 2015). Insignificant results can be caused by a smaller proportion of samples at the age of <40 years so that when tested it can result in insignificant results.

Analysis of the Relationship between Breast Cancer Stage and Breast Cancer Treatment Outcomes of Luminal Subtype B at RSUP DR. M. Djamil Padang

In this study, the treatment outcomes of breast cancer patients of luminal B subtype died the most at the local advanced stage, which was 40%. There was a significant association between the stage and the outcome of breast cancer treatment subtype luminal B. DFS in the advanced stage group was also found to be lower where the mean DFS in early stage patients was 52.8 months while in the advanced local stage was 43.65 months with a significant association between the stage and DFS. In addition to DFS, the OS in this group is also lower. The mean OS in early stage patients was 45.3 months while in advanced locally stage patients it was 38.51 months with a significant difference between the two.

The results of this study are supported by the findings of Abdullah et al. in 2013 the stage was associated with overall survival in Malaysian women with breast cancer, where advanced stage had a low survival rate compared to early stage. Advanced stages show the progressivity of diseases that have invaded many cells of the body. In addition, the involvement of KGB and distant metastases indicates that cancer cells have spread to several other body cells in different organs and a marker of the occurrence of metastatic barrier barrier (KGB) damage. This leads to the increasing difficulty of eradication of cancer cells that complicate the success of therapy in breast cancer patients of luminal subtype B (Gómez-Acebo et al., 2020).

Analysis of the Relationship of Staging Histology with Breast Cancer Treatment Outcomes of Luminal Subtype B at RSUP DR. M. Djamil Padang

In the treatment outcome, breast cancer patients of luminal subtype B died the most at grade 2, which was 40%. A significant association was found between tumor histological grade and

treatment outcomes in breast cancer of luminal subtype B. The mean DFS in a row according to grade is as follows: grade I obtained 60 months, grade II obtained 47.12 months, and grade III obtained 32.73 months. There is a significant difference between histological grade and DFS in breast cancer patients of luminal subtype B. The mean OS successively according to grade is as follows: grade I obtained 51.25 months, grade II obtained 50.86 months, and grade III obtained 37.27 months. There is a significant difference between histological grade and the OS of breast cancer patients of luminal subtype B. The histological grade has repeatedly proven to be a strong and independent prognostic factor where the higher histological grade shows the properties of the cell that are increasingly different from the original properties so that it will be more difficult to control its development which causes its poor prognosis in patients. This is in accordance with research by Ehinger et al. in 2016 which stated that breast cancer subtype luminal B was mostly in G2 or G3 (87%) and was associated with poor survival (Ehinger et al., 2017). Research conducted by Ehinger also states something similar, that the higher the histlogy grading of a tumor, the worse the prognosis.

Analysis of the Relationship between ER Expression and Breast Cancer Treatment Outcomes of Luminal Subtype B at RSUP DR. M. Djamil Padang

In this study, it was found that breast cancer patients of luminal subtype B died the most in ER positive, which was 40% but in this study there was no statistically meaningful relationship between ER expression and treatment outcomes. The mean DFS in breast cancer patients of luminal subtype B ER negative was 46.38 months while in ER positive it was 45.34 months and no significant difference was found between the two. The mean of OS in breast cancer patients of luminal subtype B ER negative was 46.69 months and ER positive was 38.85 months, however this difference was not statistically significant. This is in accordance with the findings of Karakolevska-Ilova et al. in 2021 which stated that estrogen receptor expression did not show prognostic significance for OS in breast cancer subtype luminal B. In the study, it was found that the OS of patients with ER expression >10% after 70 months decreased gradually while all patients without or low ER expression lasted longer (more than 100 months) so it can be concluded that ER is not an independent factor that determines the prognosis of the patient luminal subtype B breast cancer (Karakolevska-Ilova et al., 2021).

Research by Rajc in 2018 found different things where Kaplan-Meier's analysis showed that low estrogen receptor positivity (ER) and PR in tumors were associated with much worse disease outcomes (OS and DFS). ER is a prognostic factor for breast cancer and a predictor of response to endocrine therapy. However, in breast cancer of luminal subtype B, other prognostic factors can influence outcomes so there are variations in the results of studies on ER expression in influencing (Rajc et al., 2018) patient treatment outcomes as mentioned in the study by Karakolevska-Ilova et al. (2021).

Analysis of the Relationship between PR Expression and Breast Cancer Treatment Outcomes of Luminal Subtype B at RSUP DR. M. Djamil Padang

In this study, it was found that breast cancer patients of luminal B subtype died the most in PR positive, which was 35% but in this study there was no statistically meaningful relationship between PR expression and treatment outcomes. This is in contrast to the findings of Utsumi et al. the 2020s that got patients with PR+ had a better prognosis. PR+ signals the patient can respond to hormonal therapy. Since PR is the end product of estrogen action where estrogen plays a role in synthesizing progesterone receptors, PR expression is generally thought to be dependent on ER activity, with a lack of PR reflecting nonfunctional ER and resistance to hormonal therapy. In addition, Utsumi et al. also stated that the absence of PR expression is inversely proportional to the status of HER2 where in luminal PR – high expression of HER2 is obtained so that it tends to have more aggressive biological properties (Utsumi et al., 2021). The difference that occurred in this study was likely that the number of patients who died more in PR+ was due to the positive PR dominance in this study so that the proportion of patients who died also became more and had an impact on the results that were contrary to the existing theory.

The mean DFS in breast cancer patients of luminal subtype B PR negative was 43.42 months while in PR positive it was 46.02 months and no significant difference was found between the two. The mean OS in breast cancer patients of luminal subtype B PR negative was 41.69 months and PR positive was 33.00 months, however this difference was not statistically significant. These results are in contrast to the 2020 findings of Utsumi et al which stated in univariate analyses, PR was identified as a significant favorable prognostic factor for DFS and OS in luminal B HER2 positive and negative. However, upon further analysis in multivariate analysis, PR is not an independent prognostic factor so the conclusion in the study is the same as that of this study that the survival of luminal B patients is not influenced by progesterone receptors independently because as mentioned by Utsumi et al where PR is inversely proportional to HER2 expression which means that in negative PR a higher HER2 is found, it can be drawn that PR contributes to prognostic factors through its effect on other, stronger prognostic factors one of which is HER2 (Utsumi et al., 2021).

Analysis of the Relationship of Ki67 Expression with Breast Cancer Treatment Outcomes of Luminal Subtype B at RSUP DR. M. Djamil Padang

In this study, it was found that breast cancer patients of luminal subtype B died the most in Ki67 in the range of 20-40%, which was 44% but in this study there was no statistically meaningful relationship between Ki67 expression and treatment outcomes. The mean DFS in breast cancer patients of luminal subtype B with Ki67 was in the range of 20-40%, was 45.94 months while in Ki67 >40% was 39.28% of the month and no significant difference was found between the two. Similarly to DFS, there was no significant difference between OS and Ki67 with mean OS in breast cancer patients of luminal subtype B with Ki67 being in the range of 20-40%, was 39.90 months and in Ki67 >40% was 39.42% month. Similar findings were obtained by Karakolevska-

Ilova et al in 2021 which could not prove Ki-67 as a prognostic factor for survival in breast cancer of luminal subtype B (Karakolevska-Ilova et al., 2021).

This is different from a study by Kim et al in 2013 which stated that Ki-67 expression is related to important prognostic factors both in terms of RFS and OS in luminal type breast cancer patients, but in this study, Ki-67 assessments were distinguished into negative and positive, not distinguished from levels so it was concluded that the presence of Ki-67 factors in breast cancer greatly influenced the development of the disease, but the difference in levels above 20% did not have significant influence (Kim et al., 2013). Thangarajah in her 2017 study also confirmed this where strict cut-off values are not suitable for distinguishing between high and low risk patients and their response to the treatment of breast cancer subtype luminal B (Thangarajah et al., 2017). In addition, from the factor of the number of unbalanced samples can also cause bias where in this study the proportion of patients with Ki67 which is in the range of 20-40% more, namely 93% and Ki67 >40% only 7% so that this can result in bias.

Analysis of the Relationship of HER2 Expression with Breast Cancer Treatment Outcomes of Luminal Subtype B at RSUP DR. M. Djamil Padang

In this study, breast cancer patients of luminal B subtype died the most in HER2 positive, which was 46% and in this study a statistically meaningful relationship was found between HER2 expression and treatment outcomes. This is in line with the findings of mean OS and mean DFS in breast cancer patients of luminal subtype B. In HER2 negative OS is longer at 58.32 months while in positive HER2 it is shorter at 32.69 months with a significant difference between the two. Mean DFS in breast cancer patients of luminal subtype B HER2 positive was also found to be shorter at 32.85 months and HER2 negative longer at 50.38 months, and this difference was statistically significant.

Worse outcomes in Luminal B HER2 positive were also found in a 2009 study by Cheang et al that obtained luminals with HER2-positive statistically significant associated with breast cancer with recurrence-free survival and disease-specific survival in all adjuvant systemic treatment categories (Cheang et al., 2009). Li et al in 2016 also stated the HER2 gene is an important prognostic indicator for breast cancer patients. In patients with luminal B breast cancer, compared to patients in the HER2+ subgroup, the median survival of disease progession-free from the HER2− subgroup was longer and this difference was statistically significant (Li et al., 2016).

HER2 has been recognized as a proto-oncogene located on chromosome 17q. In addition, HER2 encodes a 185 kDa transmembrane phosphoglycoprotein with tyrosine kinase activity which is mainly found on the surface of tumor cells so that the higher expression of HER indicates higher tumor cell activity. This fact is reinforced by her2 overexpressed in almost 25% of invasive breast carcinomas with a poor prognosis and having amplification of 500,000-2,000,000 receptors of each tumor cell thus causing a poor prognosis and shorter survival (Paramita et al., 2019).

High HER2 expression is associated with factors such as high histological grading, cell proliferation, lymph node involvement and the patient's body resistance to chemotherapy. A positive HER2 shows a protein that has a high aggressiveness to breast cancer. Over expression of

HER2 in breast carcinoma shows an increased risk for recurrence (77%) and an ugly prognosis. HER2 status can also be a predictive factor for the chemotherapy response with the use of trastuzumab therapy (Rahmatya et al., 2015).

Analysis of the Relationship between Drug Therapy and Breast Cancer Treatment Outcomes of Luminal Subtype B at RSUP DR. M. Djamil Padang

In this study, it was found that breast cancer patients of luminal B subtype died the most in patients treated with non-taxan base, which was 39% and in this study a statistically meaningful relationship was found between drug choice and treatment outcomes. The mean DFS in breast cancer patients of luminal subtype B treated with taxan base was 49.81 months and non taxan base was 43.44 months, and this difference was statistically significant. Mean OS in breast cancer patients of luminal subtype B who were treated with a longer taxan base of 53.68 months while in non taxan base it was shorter at 33.36 months and a significant difference was found between the two (Wilson et al., 2022).

This can be attributed to the finding of a relationship between amplification of the HER2 gene or overexpression of HER2, so that the paradigm of breast cancer treatment has changed. Therefore, a targeted therapy against HER2 was specifically developed, namely Traztuzumab which is a monoclonal antibody humanized for the HER2 protein which is able to inhibit the growth of breast cancer cells so that it has the potential to treat breast cancer. In the absence of targeted therapy in patients with breast cancer subtype Luminal B HER2 (+), it can be a result of the low survival rate of patients in this study.

This is supported by a 2019 literature review of Wilson et al where compared to non-taxan therapies namely cyclophosphamide, doxorubicin, methotrexate and fluorouracil, taxan-base therapy can improve survival and decrease patient recurrence. In this study, it was also stated that a total analysis was carried out on 39,180 women and obtained a regimen containing taxane improved the OS when compared to controls that did not contain taxane (Albain et al., 2012).

The same was true in DFS assessments in 41,909 women where taxane-containing therapy improved disease-free survival (DFS) compared to controls. The mechanism of *taxane-base* therapy in improving the survival of breast cancer patients of luminal subtype B is to inhibit the dynamics of microtubulers that support their polymerization so that it can produce cell *cycle arrest* in phase G2 and phase M which leads to cell death (Gradishar, 2012; Wilson et al., 2022).

Analysis of the Most Dominant Factors in Influencing the Outcome of Breast Cancer Treatment of Luminal Subtype B at RSUP DR. M. Djamil Padang

Based on multivariate analysis in this study, it was found that the factor that most influenced the outcome of breast cancer treatment in sub-type B was HER2 expression where this variable has the largest odd ratio, which is 7, which means that the presence of positive HER2 expression is seven times more at risk of having an outcome which is worse. The very influential role of HER2 in the prognosis of breast cancer is explained by Rabinovich et al. in 2018 where mentioned Flow cytometry showed a higher cell frequency of CD44+/CD24- in HER2+ cell line, which

showed HER2 featuring the ability to increase the proportion of CD44 +/CD24-stem cells. In the cancer stem cell model, tumors originate from a small population of stem cells that lose the regulation of the self-renewal process. The consequence is that the differentiation and growth of these cells is accompanied by genetic and epigenetic changes. Resistance to therapy can be attributed to the evolution of these clones. Some of these cells can be identified by cell surface markers, such as the presence of CD44 and the absence of CD24 markers (CD44+/CD24- phenotype). CD44 and CD24 function in inhibiting the invasion and metastasis of breast cancer cells so that the CD44+/CD24- phenotype is clearly associated with the invasion. The development of HER2 target agents such as trastuzumab has altered the prognosis of tumors expressing high HER2 in recent years, especially when used in neoadjuvant settings (Rabinovich et al., 2018).

The results of this study are in line with the findings by Cooke T et al. in 2001 which stated that HER2 status is a prognostic and predictive factor against DFS and OS where patients with HER2 positive have poor disease outcomes. In addition, HER2 is also used as a predictor of the therapeutic response, which can see an increased risk to the aggressiveness of the tumor, and a rapid recurrence (Rabinovich et al., 2018).

CONCLUSION

In this study, it was found that most breast cancer patients at RSUP Dr. M. Djamil Padang had CPI results of Luminal B subtype. Most breast cancer patients of luminal B subtype are over 40 years old (83%), have advanced local stage (80%), have a histological grade of G2 (81%), have a positive ER (87%), have a positive PR (79%), have a Ki67 proliferation index of 20-40% (93%), are treated with non taxane base (68%) and as many as 47% die. There was no statistically meaningful association between age and breast cancer treatment outcomes with a p value of > 0.05, which was 0.368. No meaningful relationship was found between age with DFS and OS (p values of 0.260 and 0.905 respectively).

There is a statistically meaningful relationship between stage and treatment outcome with a p value of 0.009. A meaningful relationship was found between the stage of breast cancer with DFS and OS with p values of 0.037 and 0.021, respectively. There is a statistically meaningful relationship between histological staging and treatment outcomes with a p value of 0.023. Found a meaningful relationship between staging with DFS and OS with p-values of 0.028 and 0.036 respectively

There was no statistically meaningful relationship between ER expression and treatment outcomes with a p value of 0.731. There was no meaningful relationship between the expression ER with DFS and OS with p values of 0.997 and 0.996, respectively. There was no statistically meaningful relationship between PR expression and treatment outcomes with a p value of 0.215. no meaningful relationship was found between PR expressions with DFS and OS with p values of 0.633 and 0.253. There was no statistically meaningful association of the Ki67 proliferation index with a treatment outcome with a p value of 0.215. No meaningful relationship found between Ki67 expressions with DFS and OS with p values being 0.422 and 0.903 respectively.

There is a statistically meaningful relationship between HER2 Expression and Treatment Outcomes with a p-value of 0.000. A meaningful relationship was found between the expression HER-2 with DFS and OS with p value both being 0.000. There is a statistically meaningful association between the type of therapy and the Treatment Outcome with a p-value of 0.000. There is a meaningful relationship between the type of therapy with DFS and OS with the p-value of both being 0.000. Multivariate analysis showed HER2 and type of therapy were factors that were significantly associated with the outcome of treatment of cancer patients with HER2 being the dominant factors.

It is hoped that further research will be carried out with a larger number of samples and balanced between the variables compared in order to avoid sample bias. More research needs to be done by separating the prognostic factor assessment between Breast Cancer subtype Luminal B HER2 negative and HER2 positive. This research can be used as a guide in the flow of diagnosis and management of breast cancer patients of the Luminal B subtype.

It is hoped that there will be a policy to make HER2 targeted therapy one of the main therapies in the treatment of breast cancer patients of the Luminal B HER2+ subtype due to the poor prognosis of Luminal B HER2(+) without targeted therapy treatment as found in this study. Also, the researchers expect future research to dig deeper into this matter to add even more insightful reference regarding luminal B breast cancer and its treatments.

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