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The Effects of Tamoxifen and Chemotherapy after Surgery on the Recurrence and Survival of Breast Cancer Patients with Positive Hormone Receptor: A Meta-Analysis

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ABSTRACT

Background: Breast cancer is the most common type of cancer suffered by women in the world. The combination of tamoxifen and chemotherapy significantly reduces the risk of recurrence and mortality in breast cancer patients. This study aimed to analyze how effective the combination of tamoxifen and chemotherapy after surgery to reduce the risk of recurrence and mortality in breast cancer patients with positive hormone receptor.
Subjects and Method: This study used systematic review and meta-analysis. The researcher collected articles from the Pubmed journal database. The subjects of the study were women with breast cancer after surgery. The dependent variable was recurrence and survival (mortality). The independent variables were tamoxifen and chemotherapy. Data were analyzed based on the fixed and random effects model using RevMan 5 software.
Results: There were 3 articles with 3,761 women who were involved in the analysis process. The combination of tamoxifen and chemotherapy could reduce the risk of recurrence in women with positive hormone receptor (ER+) breast cancer (HR=0.68; 95%CI=0.58 to 0.80; p=0.001). The combination of tamoxifen and chemotherapy showed weak and non-significant decreasing trend in reducing the risk of mortality in women with ER+breast cancer (HR=0.87; 95%CI=0.73 to 1.03; p= 0.11).
Conclusion: The combination of tamoxifen and chemotherapy in women with ER+ breast cancer is effective in reducing the risk of recurrence. However, it does not increase survival.

Keywords: tamoxifen, chemotherapy, breast cancer.

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BACKGROUND

Breast cancer is the most common type of cancer suffered by women in the world. Breast cancer is ranking first in African, Europe, and Asia continents with the highest mortality rate in women (IARC, 2018). Breast cancer is also the largest number type of cancer with the second largest number of new cases (11.6%) after lung cancer in the world (Bray et al., 2018). Breast cancer is the type of cancer that causes the most common deaths in Indonesia with the total number of 19,731 in 2014 (Listyawardhani et al., 2018). Adjuvant therapy such as chemotherapy and hormonal therapy is often recommended by oncologists as a treatment for breast cancer (Cloud and Esfahani, 2018)

Chemotherapy has an important role in the last two decades. It is a treatment for breast cancer in reducing tumor mass before surgery. In addition, it prevents the tumor for coming back after surgery (EBCTCG, 2012; Akram and Siddiqui, 2012).

Tamoxifen has been extensively studied and proven effective for treating early-stage breast cancer (Jankowitz and Davidson, 2013). The combination of tamoxifen and chemotherapy can increase survival by reducing the risk of mortality and recurrence (Bramwell et al., 2010).

This study aimed to compare the effectiveness of the combination of chemotherapy with tamoxifen and the effectiveness of chemotherapy only to reduce the risk of recurrence and improve survival in women with breast cancer with positive hormone receptor.

SUBJECTS AND METHOD

1. Design of the Study

This study used systematic review and meta-analysis design. It referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA). The researcher collected articles from the Pubmed journal database using the keywords such as "tamoxifen", "chemotherapy", and "breast cancer".

2. Inclusion Criteria

The inclusion criteria were: 1) Intervention was a combination of tamoxifen and standard chemotherapy; 2) Control was chemotherapy only; 3) The design of the study was RCT; 3) The articles used English language; 4) The results of the study were recurrence and survival.

3. Population and Sample

The population of the study was women with breast cancer of ER+ type who had undergone surgery (mastectomy). This study involved 4 clinical trials with 3761 women as the subjects of the study.

4. Variables of the Study

The dependent variable was the combination of recurrence and survival. The independent variables were the combination of chemotherapy and hormonal.

5. Operational Definition of Variables

Intervention of this study was the combination of chemotherapy and tamoxifen. Control was chemotherapy. Recurrence was the second cancer cell after the intervention. Survival was the death occurred due to all causes after the intervention.

6. Data Analysis

The data were analyzed using RevMan 5. The data were described using the effect size hazard ratio with 95% confidence interval (CI). The value of $p<0.05$ indicated that the result was statistically significant.

RESULT

After searching for the articles in Pubmed database, 336 articles were found.

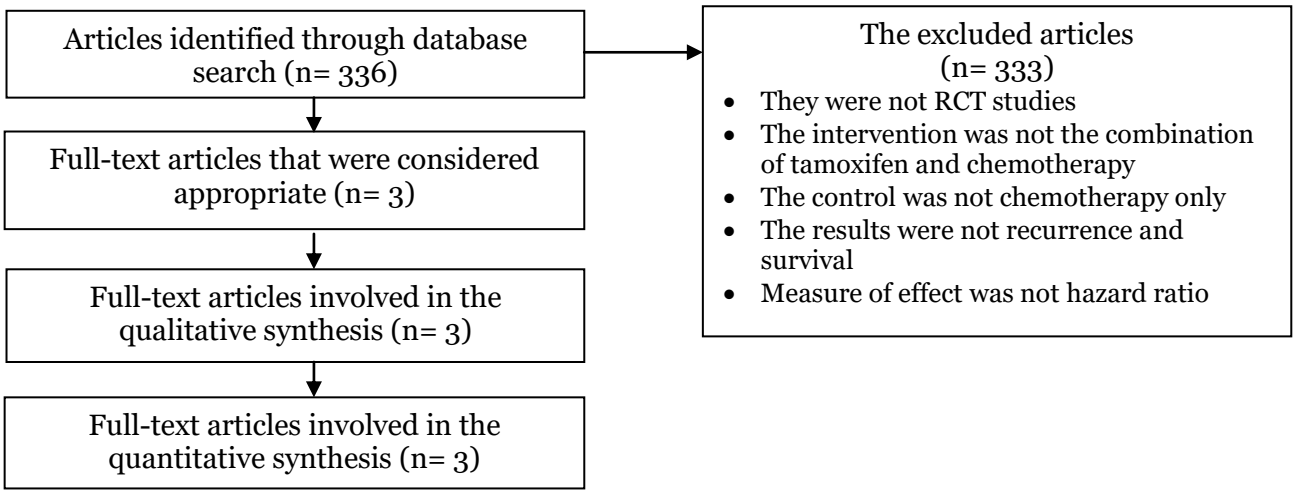

Figure 1. Research Flow

There were 333 articles that were excluded because they did not meet the inclusion criteria. There were 3 full text articles in quantitative and qualitative analysis (Figure 1). There were 3 articles in the analysis of the variable of recurrence (Table 1) and 3 articles on the variable of survival (Table 2). The intervention followed the operational standards for chemotherapy and tamoxifen that were used globally (Table 3).

Table 1. The result of the study on the variable of recurrence in each article analyzed.

No	Writer	Total number of patients	Total number of recurrence (n)	Hazard Ratio	95% CI	p
1	Bramwell (2010)	Intervention= 252 Control= 253 Total=505	Intervention = 252 Control = 253	0.82	0.61-1.11	0.18
2	Morales (2006)	Intervention = 233 Control = 258 Total= 491	Intervention = 233 Control = 258	0.68	0.50-0.93	0.014
3	International Breast Cancer Study Group (2006)	Intervention = 365 Control = 370 Total= 735	Intervention =108 Control =164	0.59	0.46-0.75	0.001

Table 2. The result of the study on the variable of survival in each article analyzed.

No	Writer	Total number of patients	Total number of mortality (n)	Hazard Ratio	95% CI	p
1	Bramwell (2010)	Intervention =252 Control = 253 Total= 672	Intervention = 252 Control = 253	0.83	0.58-1.18	0.12
2	Morales (2006)	Intervention = 233 Control = 258 Total= 491	Intervention = 233 Control = 258	0.89	0.69-1.15	0.001
3	International Breast Cancer Study Group (2006)	Intervention = 365 Control = 370 Total= 735	Intervention =68 Control =78	0.86	0.62-1.19	0.36

Table 3. The specifications of the therapy given to each article analyzed.

No	Writer	Therapy in the intervention group	Therapy in the control group	Duration of therapy
1	Andersson (1999)	• 9 cycles of the CMF. • 30 mg of tamoxifen a day	• 9 cycles of the CMF.	Chemotherapy and hormonal therapy were given for 1 year.
2	Bramwell (2010)	• 6 CMF. • 6 cycles of the CEF. • 4 cycles of the AC. • 20 mg tablet of tamoxifen.	• 6 cycles of the CMF. • 6 cycles of the CEF. • 4 cycles of the AC. • Placebo.	Chemotherapy was given for 14 weeks. Tamoxifen was given on the 8th day of the chemotherapy for 5 years.
3	Hutchins (2005)	• 6 cycles of the CMF. • 6 cycles of the CAF. • 20 mg tablet of tamoxifen.	• 6 cycles of the CMF • 6 cycles of the CAF	Tamoxifen was given on the 29th day in the cycles of chemotherapy.
4	International Breast Cancer Study Group (2006)	• Doxorubicin, cyclophosphamide, methotrexate, fluorouracil. • Epirubicin, cyclophosphamide, methotrexate,	• Doxorubicin, cyclophosphamide, methotrexate, fluorouracil. • Epirubicin, cyclo-	Chemotherapy was given for 21 days, then it was given again after 28 days since the first therapy. Tamoxifen was given

		fluorouracil. • 20 mg tablet of tamoxifen.	phosphamide, methotrexate, fluorouracil.	after the cycle of chemotherapy was complete, for 5 years.
5	Morales (2006)	• 6 CMF. • 4-6 cycles of CAF, CEF, FAC or FEC. • 20 mg tablet of tamoxifen	• 6 CMF •4-6 cycles CAF, CEF, FAC atau FEC.	Tamoxifen was given in the last 2 weeks of the cycle of chemotherapy, for 3 years.
6	Ingle (1989)	• 10 cycles CFP. • 10 mg tamoxifen 2 times a day.	• 10 cycles CFP.	Chemotherapy and tamoxifen were conducted for 6 weeks.
7	Tormey (1990)	• CMF. • CMFP. • 10 mg of tamoxifen 2 times a day.	• CMFP.	Chemotherapy and tamoxifen were conducted for 28 days.

1. Recurrence

a. Forest Plot

The combination of chemotherapy continued with tamoxifen showed the significant result compared to chemotherapy only in reducing the risk of recurrence in women with breast cancer with positive hormone receptor (HR=0.68; 95%CI=0.58 to 0.80; p= 0.001) (Figure 2). Based on the result of the analysis, the value of heterogeneity obtained was low (I^2=28%). Therefore, a fixed effect model was used.

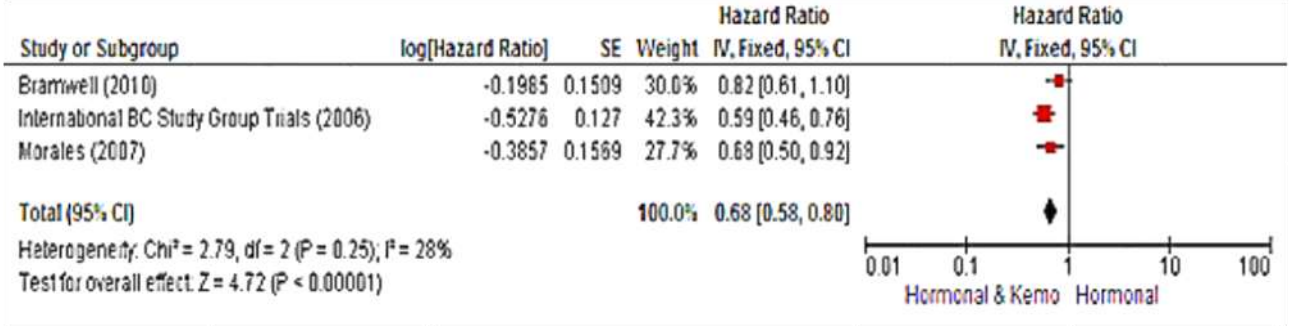

Figure 2. Forest plot of recurrence as the variable

b. Funnel Plot

The funnel plot on recurrence showed that there was a publication bias on the analysis. It was indicated by the asymmetrical location of the circles on the right and left sides of the line. The small circles represented each article in the analysis (Figure 3).

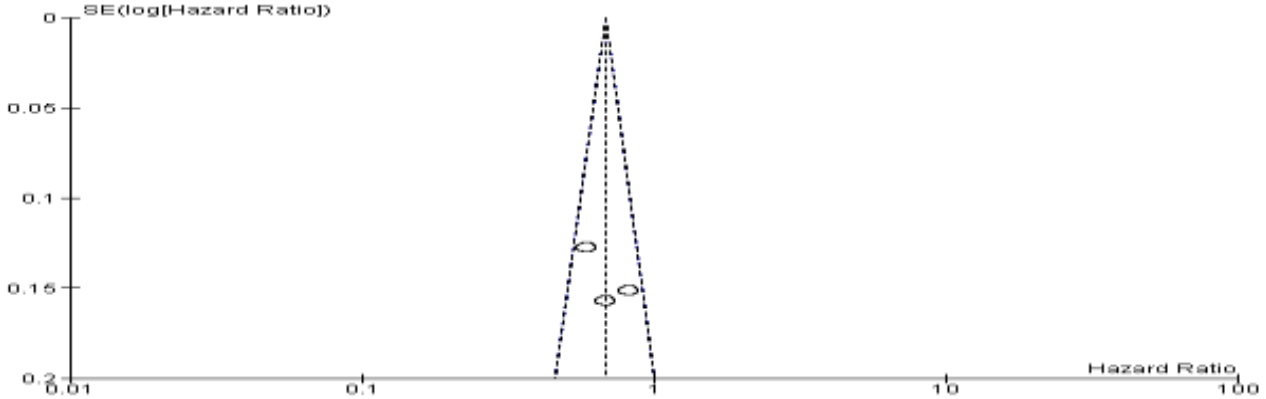

Figure 3. Funnel plot of recurrence as the variable

2. Survival

a. Forest Plot

The comparison between the combination of chemotherapy and tamoxifen did not show the significant result compared with chemotherapy only in improving survival by reducing mortality in women with breast cancer with positive hormone receptor (HR=0.87; 95%CI=0.73 to 1.03; p=0.11) (Figure 4). Based on the result of the analysis, the value of heterogeneity was very low (I^2=0%). Therefore, a fixed effect model was used.

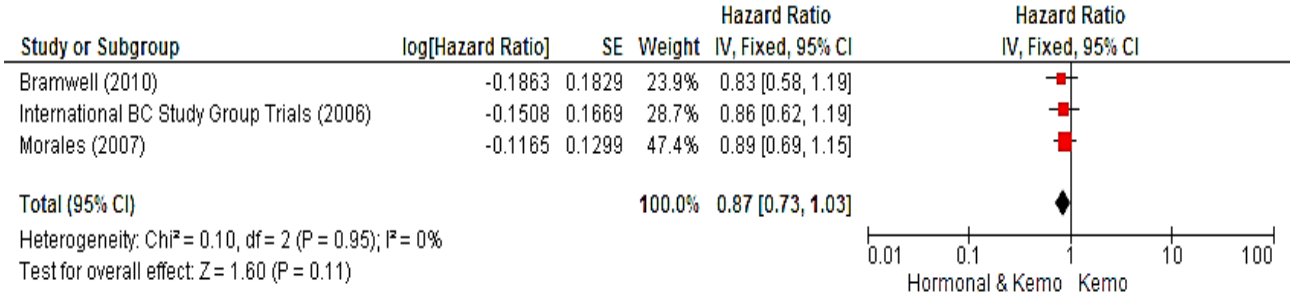

Figure 4. Forest plot of survival as the variable

b. Funnel Plot

Funnel plot on survival showed that there was no publication bias on the result of the analysis. It was indicated by the circles location that was in the diameter symmetrically (Figure 5).

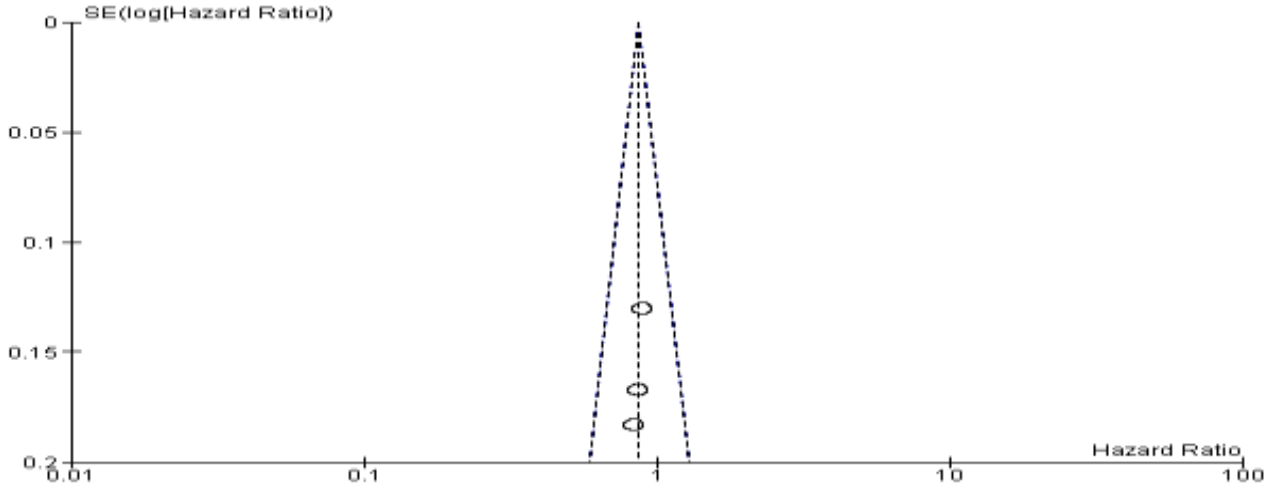

Figure 5. Funnel plot of survival as the variable

DISCUSSION

Based on the global data, breast cancer is the most common type of cancer experienced by women (Yu et al., 2017). According to Burstein et al. (2014), the most common type of breast cancer is positive hormone receptor (60-75%). Positive hormone receptor is the breast cancer with positive estrogen receptor (ER+) or positive progesterone receptor (PR+) (Tang et al., 2016).

Chemotherapy aims to reduce tumor mass before surgery and prevent tumor for coming back after surgery. It is caused by HIF-1α which is more commonly found (hypoxia triggering factors) in cancerous tissue after chemotherapy than before chemotherapy (Berman, 2015; Wiraswesty

et al., 2016; Ruihua et al., 2017). Tamoxifen has been extensively studied and proven effective for treating breast cancer. Based on a meta-analysis study, the use of tamoxifen for 5 years in breast cancer patients with ER- had a positive significant effect in reducing the risk of recurrence within the first 10 years. In addition, it decreased almost one-third the mortality rate within the first 15 years. It occurred due to the antitumor effect on tamoxifen. How the amoxifen's system work is by blocking estrogen hormone receptor in breast tumor, thus reducing the circulation of the hormone estrogen in breast tissue which is useful for inhibiting the growth of cancerous tissue (Davies et al., 2011; Jankowitz and Davidson, 2013; Rubin, 2015).

Giving tamoxifen after chemotherapy increased the cure rate of breast cancer patients who had positive endocrine receptor (ER+). Giving tamoxifen for 3 years after chemotherapy had benefit towards the recurrence and survival in breast cancer with positive hormone receptor. Tamoxifen has benefits on the breast cancer with positive receptor hormone, except the breast cancer with negative receptor hormone (Morales et al., 2006; International Breast Cancer Study Group, 2015; Hutchins et al., 2015).

Based on the result of the analysis, the combination of chemotherapy and hormonal was more effective than chemotherapy only in reducing recurrence towards breast cancer (HR=0.68; 95%CI= 0.58 to 0.80). This result was statistically significant (p=0.001). It had a low heterogeneity value (I^2=28%), so that the analysis used fixed effect model. This is in accordance with a study conducted by EBCTCG (2012) that both therapies (chemo and endocrine) could increase disease free survival by reducing the risk of recurrence.

Based on the result of the analysis, the combination of chemotherapy and hormonal was more effective than chemotherapy only in reducing mortality, thus increasing survival in breast cancer (HR= 0.87; 95%CI=0.58 to 0.80). This result was statistically non-significant (p=0.11) and had low heterogeneity value (I^2=0%), so that the analysis used fixed effect model. The result is in accordance with a study conducted by Fisher et al. (2001) that the combination of chemotherapy continued with tamoxifen had less significant effect in reducing the risk of mortality in breast cancer.

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This study did not receive financial assistance from any agency or company.

AUTHOR CONTRIBUTION

Trisakti Halimah Delimasari, the main researcher who played a role in selecting title, finding and collecting data of the study. Didik Tamtomo, played a role in providing ideas related to the theory in the discussion. Bhisma murti, played a role in analyzing data of the study.

CONFLICT OF INTEREST

The study did not have any conflict of interest related to the publication of this article.

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