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Original Research Article

Outcome and response rate in post neoadjuvant chemotherapy for breast cancer in a tertiary hospital in Malaysia

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ABSTRACT

Background: The use of preoperative chemotherapy also increased the rate of breast conserving surgery in breast cancer. This study aims to assess the type of chemotherapy and biological markers that associated with pathological complete response in our population.
Methods: This is a data analysis involving breast cancer patients confirmed pathologically that underwent neoadjuvant chemotherapy in Hospital Raja Perempuan Zainab II from January 2018 to December 2021. Retrospective sampling was done using Sistem Pengurusan Pesakit (SPP) which is a hospital-generated database. All patients were given standard chemotherapy regimens.
Results: A total of 59 patients enrolled in this study. Half of the patients were luminal A (48%), luminal B and triple negative breast cancer (TNBC) were both 23%. All patients received antracyclin as neoadjuvant regime and 54% had a combination with Docetaxel. Only 1 patient achieved pCR which was TNBC, given Antracyclin + Taxane regime. Tumour reduction >90% highest in TNBC group and using FEC regime. Factors associated with survival were age and miller payne grade. The only pCR was achieved in triple negative breast cancer as being showed by previous study. Tumour loss with more than 30% is equal comparing Antracyline only group and Antracyline + Taxane group.
Conclusions: Antracyline + Taxane regime chemotherapy is still the regime of choice for neoadjuvant chemotherapy in breast cancer. Triple negative breast cancer patients should receive preoperative chemotherapy as they will have a higher rate of pCR.

Keywords: Breast cancer, Neoadjuvant, Outcome, Disease free survival, Recurrence

INTRODUCTION

The use of preoperative chemotherapy also increased the rate of breast conserving surgery in breast cancer. This study aims to assess the type of chemotherapy and biological markers associated with pathological complete response in our population. Breast cancer has become the number one cancer in females in Malaysia. Surgical management has significantly progressed in invasive breast cancer from radical mastectomy to breast conserving surgery, especially in early breast cancer. The use of neoadjuvant chemotherapy has increased the rate of breast conserving surgery in this type of patient. Neoadjuvant chemotherapy was first used for inoperable locally advanced breast cancer to downstage the tumour.[1] Neoadjuvant chemotherapy in operable breast cancer aims to have a pathological complete response thus improving the outcome.

Management of breast cancer has involved chemotherapy since the 1960s. Many trials have been conducted to study the effectiveness of chemotherapy. Preoperative chemotherapy has been increasingly used and many large clinical trials have demonstrated that neoadjuvant chemotherapy has benefits for patients with operable

breast cancer.[2,4-6,9-12] Given preoperative chemotherapy helps to predict tumour response to which chemotherapy regime, early cessation of ineffective chemotherapy drugs, and pathological complete response (PCR) to chemotherapy can be used to assess survivor risk.[12] It also increases the rate of breast conservation therapy in operable breast cancer.[2]

Most patients who underwent neoadjuvant chemotherapy are in locally advanced breast cancer where simple mastectomy cannot be performed. In current practice, the use of neoadjuvant had become more useful in setting early breast cancer.[2,9,11] Response of each cycle of chemotherapy must be done accurately to make sure the regime given is optimum to achieve pathological complete response. In cases that tumour did not respond after the second or third cycle of chemotherapy, further assessment is needed.[14] In early breast cancer, if the tumour did not respond well to chemotherapy, surgery is indicated as the definitive treatment.

Response to neoadjuvant chemotherapy can be assessed by clinical assessment, radiological examination and histopathological examination (HPE). Clinical assessment should be done each cycle after chemotherapy and document the size of the lump and lymph nodes. Radiological investigations like ultrasound (US), Mammography (MMG), and MRI can be used to assess chemotherapy response. Ultrasonography has better accuracy compared to mammography in assessing residual tumour after neoadjuvant chemotherapy. When both imagine demonstrating no residual tumour, the likelihood of pathological complete response is 80% whereas when only a single method is used (either US alone or MMG) the detection rate is only 53.3%.[7] MRI is a better modality to assess tumour response compared to US and mammogram however this modality is limited and higher cost.[8]

Histopathological specimen is the most important tools for evaluation by looking for pathological complete response (PCR) using Miller Payne Grading (Table 1). This grading was used to classify the chemotherapy response in breast cancers.

Few landmark trials have compared a few types of chemotherapy regimens and also comparing overall survival (OS) and disease-free survival (DFS) in pre and post-operative chemotherapy. NSABP B18 trial compared pre and post-surgery chemotherapy using AC regime while NSABP B27 trial added Taxane group using Docetaxel. From this study, adding Taxane group has significantly increased clinical complete response (CCR) and pathological complete response (PCR). Preoperative chemotherapy also increases DFS in patients with clinical response to chemo, according to this study.[3,4,6]

PCR has been used as an end point prediction for clinical important such as disease-free survival (DFS) and overall survival (OS). PCR is associated with increased DFS in triple negative breast cancer, HER-2 positive with hormonal receptor negative, HER-2 positive, Hormon receptor positive in high grade tumour (G3) and also hormone negative breast cancer.[4] However, an increase PCR does not significantly predict improve in DFS and OS.

In another large study, EORTC 10902, preoperative chemotherapy can be given safely in early breast cancer. This study used FEC regime with endpoint of rate of breast conserving surgery, DFS, OS and tumour response to chemotherapy.[2] In this study rate of PCR was 20%. Breast Cancer International Research Group (BCIRG) conducted a study involving 20 countries using 3 types of chemotherapy regimes, FEC, FAC and TAC. From this study TAC has shown risk of neutropenia and anaemia compared to FEC regime.[13,14] TAC has higher pCR compared to FAC/FEC which is 20% compared to 13%.[17]

This study aims to assess the type of chemotherapy and biological markers that are associated with pathological complete response in our population.

METHODS

This is an observational retrospective study involving all confirmed breast cancer patients by histopathology who underwent definitive surgery after neoadjuvant chemotherapy in Hospital Raja Perempuan Zainab II (HRPZII) from 01 January 2018 to 31 December 2021. Retrospective sampling using SPP (hospital generated data based) and all patients that were admitted for surgery after neoadjuvant chemotherapy. The chemotherapy regime given were standard chemotherapy but different regime based on surgeon and oncologist preferences. The study involved all patients age more than 18 years old and undergoing surgery after chemotherapy. However, patients that refused surgery after chemotherapy, and patients with disease progression despite chemotherapy were excluded from the study.

Pathological complete response was defined as the absence of cancer cells in the breast and lymph nodes after treatment. Clinical complete response was considered when clinically and imaging showed no residual tumour. Disease-free survival was defined by time from treatment to disease recurrence and overall survival was considered from time from treatment to death. Data were collected from sistem pengurusan pesakit (SPP) local hospital database, including demographic data, clinical history and examination, chemotherapy regime used, response after completed chemotherapy by clinical assessment, laboratory result (especially histopathological examination (HPE) result) and also imaging. Additional or incomplete data were retrieved from the folder in the record office. Clinical and histopathological analyses were used to determine treatment response following neoadjuvant chemotherapy. HPE reports were based on Miller Payne criteria to determine response. We obtained

ethical approval from National Medical Research Register of Malaysia; (NMRR ID-21-02007-3QY).

Statistical analysis was done using IBM statistical package for the social sciences (SPSS) statistics 22 software. A p value of <0.05 will be taken as statistically significant at a confidence level of 95%. All the numerical data will be presented as mean (SD) while categorical data will be expressed as number (%). The relation between different pathological responses (Miller Payne) with different subtypes of breast cancer and types of chemotherapy was analyzed using Chi-square. Factors that influence mortality were analyzed using the spearman rank correlation coefficient.

RESULTS

A total of 59 patients were included in this study. All are female patients diagnosed with breast cancer and received neoadjuvant chemotherapy and surgery performed from 01 January 2018 until December 2021. Most of the patients are of Malay ethnicity and only 1 Chinese patient as the Kelantan population has a majority of Malay. Patient age ranges from 25 to 69 years old with mean age is 51 years old. Half of the study population was luminal A (48%), while luminal B and triple negative breast cancer were both 23%. Only 12% of patients underwent breast conserving surgery while the rest had mastectomy done. Early breast cancer patients were only 12 percent (stage I and II), while locally advanced (stage III) was 40% and metastatic breast cancer (stage IV) was 47%. This is because most of our patients presented with locally advanced breast cancer and metastatic breast cancer. All patients received Antracyline as neoadjuvant chemotherapy, 54% had a combination with the Taxane group. There are various regimes used. Out of 59 patients included in the study, only 1 patient achieved a pathological complete response. However, patients with partial response with Miller Payne grade 3 and 4 were half of the patients (57.2%). Follow-up time range of 6-54 months.

There is only 1 patient with pCR which is TNBC subtype and received a combination of Antracyline and Taxane group (AC +T regime). This patient presented T4bN2M1 disease. The highest ypN0 was in TNBC group (12.7%). Tumour reduction >30% were not significant comparing each breast cancer subtype but highest in luminal A (33.9%), luminal B were 17.9%, in TNBC were 19.6% and HER 2 enrich tumour were 5.4%, Tumour reduction >90% highest in TNBC group (7.1%). TNBC showed more tumour response to chemotherapy compared to other subtypes however statistically there was no significant difference between all breast cancer subtypes to tumour response (Table 2).

There were only 3 patients with local recurrence after at least 1 year of follow up. Each patient has a different Miller Payne grade (grades 1, 2 and 3). There was no local recurrence among patients with Miller Payne grade 4 and 5. All mortality was associated with distant metastasis. No death during follow-up for patients without distant metastasis even though the patient has a local recurrence.

Table 1: Demographic profile of post neoadjuvant chemotherapy for breast cancer in HRPZII.

Variables	Breast cancer's patient
	Frequency, n (%)
Age (mean±SD)	51.00 (11.659)
Race	
Malay	58 (98.3)
Chinese	1 (1.7)
Subtype breast cancer	
HER2 Enrich	3 (5.1)
Luminal A	28 (47.5)
Luminal B	14 (23.7)
TNBC	14 (23.7)
Types of surgery	
BCS	7 (11.9)
MAC	47 (79.7)
MAC + TRAM	5 (8.5)
Post chemo pathological tumour	
T0	1 (1.8)
T1	4 (7.0)
T1a	4 (7.0)
T1b	2 (3.5)
T1c	6 (10.5)
T1s	1 (1.8)
T2	18 (31.6)
T3	10 (17.5)
T4b	11 (19.3)
Post chemo pathological nodes staging	
N0	19 (34.5)
N1	16 (29.1)
N2	14 (25.5)
N3	6 (10.9)
Pathological complete response	
Yes	1 (1.7)
No	58 (98.3)
Miller Payne grade (post chemo)	
Tumour no changes	13 (23.2)
Tumour <30%	10 (17.9)
Tumour 30-90%	22 (39.3)
Tumour >90%	10 (17.9)
No tumour	1 (1.8)
Patient's status	
Alive	53 (89.8)
Death	6 (10.2)

No tumour response was highest in FEC + TAC group, this is probably due to the tumour having no response from the initial regime and was changed. In this regime, all of the patient was initially started with FEC then was changed to TAC because of clinically no response. Most probably

when tumour does not respond to FEC will not respond to TAC as well.

Pathological complete response achieved in 1 patient who was given AC + T regime. Tumour loss to chemotherapy of more than 90% was highest in the FEC-only group and the same result in tumour loss of more than 30%. However, statistically, there was no significant between the chemotherapy regime toward tumour response after neoadjuvant chemotherapy (Table 6). Even though statistically no significance comparing chemotherapy types but FEC only groups have shown higher tumour response. Tumour loss of more than 30% is equal comparing Antracyline only group and Antracyline + Taxane group (Table 3).

Breast conserving surgery rate in the study were only 11.8% while Mastectomy rate was 82.4% and 1 patient underwent mastectomy + TRAM (5.9%). Out of 7 patients that underwent BCS, 5 of them were ypT1 and ypT2. T1 and T2 tumour patients that had a mastectomy were 28 patients out of 47 of the total patient that underwent mastectomy. The patient that had pathological complete response was not from early breast cancer group.

All death were post mastectomy and axillary clearance surgery. Mortality from this study was 10% (6 out of 58) with mean survival of 6 months (Table 4). Patient post MAC has slowly decrease in survival.

There is a significant association between patient status with age and Miller Payne grading. Factors that were significantly associated with survival were, patient age and Miller Payne grading. Other factors are not affected survival. Higher age is associated with poorer survival while higher miller Payne is associated with better survival (Table 5).

Table 2: The comparison of Miller Payne grade with subtype of breast cancer.

Miller Payne grade (post chemo)	Subtype of breast cancer, frequency, n (%)				χ^2 (df)	P value
	HER2 Enrich	Luminal A	Luminal B	TNBC		
Tumour less than 30%	-	13 (23.2)	6 (10.7)	4 (7.1)	3.990 (3)	0.263*
Tumour more than 30%	3 (5.4)	13 (23.2)	7 (12.5)	10 (17.9)		
No changes	0	7	3	3		
Tumour loss <30%	0	6	3	1		
Tumour loss 30-90%	1	11	5	5		
Tumour loss >90%	2	2	2	4		
pCR	0	0	0	1		

Chi-square test was applied, significant at the level of 0.05

Table 3: The comparison of Miller Payne grade with types of chemotherapy.

Miller Payne grade (post chemo)	Types of chemotherapy, frequency, n (%)		χ^2 (df)	P value
	A only (n:24)	A + T (n:32)		
Tumour no changes	4 (30.8)	9 (69.2)	1.923 (1)	0.166
Tumour <30%	4 (40.0)	6 (60.0)	0.400 (1)	0.527
Tumour 30-90%	9 (40.9)	13 (59.1)	0.727 (1)	0.394
Tumour >90%	7 (70.0)	3 (30.0)	1.600 (1)	0.206
No tumour	-	1 (100.0)	-	-

A only: Antracycline only, A+T : Antracycline and Taxane, Chi-square test was applied, significant at the level of 0.05

Table 4: Survival of metastatic breast cancer that receive neoadjuvant chemotherapy then underwent surgery.

Variables	Patient status, frequency, n (%)	
	Alive	Death
Types of surgery		
BCS + AC	7 (100.0)	-
MAC	44 (88.0)	6 (12.0)
MAC + TRAM	1 (100.0)	-
Medians for survival time		
	95% CI	
Estimate (in months)	**Lower bound**	**Upper bound**
6.0 months	3.6	8.4

Cross tabulation analysis was applied, indicator- BCS+ AC: breast conserving surgery +SLNB/ axillary clearance, MAC: mastectomy + SLNB/axillary clearance, MAC + flap: mastectomy + SLNB/axillary clearance + autologous flap (TRAM /LD)

Table 5: The Spearman matrix of study variables (n=59).

S. no.	Variables	Patient status	Age	Race	Surgery	ypT	ypN	pCR	MP
1	Patient status	1							
2	Age	-0.122*	1						
3	Race	-0.044	0.216*	1					
4	Surgery Types	0.028	0.043	0.011	1				
5	ypT	0.020	-0.035	0.191*	0.177*	1			
6	ypN	0.042	0.248*	0.219*	0.317*	0.401*	1		
7	pCR	-0.044	-0.197*	-0.017	0.011	-0.233*	-0.161*	1	
8	Miller Payne grade	0.091*	-0.118*	-0.187*	-0.057	-0.465*	-0.167*	0.240*	1

*Correlation is significant at the level 0.05 level (2-tailed)

DISCUSSION

Neoadjuvant chemotherapy was previously introduced for locally advanced non-operable breast cancer. However recent development showed benefits for early breast cancer, especially for triple-negative breast cancer and HER2-enriched tumour. Even though there was no difference in overall survival in patients who underwent neoadjuvant chemotherapy compared to adjuvant chemotherapy, previous meta-analyses have shown that pathological complete response (pCR) is associated with improved survival. According to a large study, EORTC 10902, preoperative chemotherapy using the FEC regime was given safely in early breast cancer with a PCR rate was 20%. However, in our study due to the small number of patient, only 1 (1.7%) patient achieved pathological complete response, tumour loss of more than 90% were 17%.

Breast Cancer International Research Group (BCIRG) conducted a study involving 20 countries using 3 types of chemotherapy regimes, FEC, FAC, and TAC. From this study TAC has shown a risk of neutropenia and anaemia compared to FEC regime17,18. TAC has higher pCR compared to FAC/FEC which is 20% compared to 13%16. In our study, a few patients that received TAC as the first line has side effects of neutropenic sepsis that warrant a change of regime. However, tumour responses (complete and partial) were demonstrated more in the FEC group than the TAC group even though statistically not significant. Tumour loss with more than 30% is equal comparing Antracyline only group and Antracyline + Taxane group. Although from other studies, TAC has shown more response with more side effects, however, in this study, patients have more response in the FEC regime. Those who were not responded to FEC and later changed to TAC did not show any response after the regime changed. This could be tumour itself is not responding to any chemotherapy. However, the only pCR was achieved in triple-negative breast cancer as being showed by a previous study.

Factors associated with survival were age and Miller Payne grade. Higher age is associated with poorer survival while higher Miller Payne grade is associated with better survival. Previous study showed chemotherapy response is a major parameter that predicting survival[15]. As in this study also shown that Miller Payne grade is the strongest factor that associated with survival. Mortality was 10% in the mastectomy group with overall survival of 6 months, but no mortality was observed in the breast-conserving surgery group. The recurrence rate was not analysed in this study as follow-up until a maximum of 4 years only. However, 3 (5%) patients developed local recurrence during follow-up.

Limitation in this study was the sample size is small as it was during covid time and due to no in house oncologist in our centre most of chemotherapy were manage by the surgeons. Further studies need to be continued for more patients.

CONCLUSION

Neoadjuvant chemotherapy that leads to a pathological complete response can prognosticate disease-free survival. The current regime using Anthracycline and Taxane still showed a response for neoadjuvant chemotherapy in breast cancer. Achieving pCR is the aim of every patient subjected to neoadjuvant chemotherapy however if pCR not achieved, the rate of tumour response can still be used as a survival prognosis.

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REFERENCES

1. De Lena M, Varini M, Zucali R, Rovini D, Viganotti G, Valagussa P, et al. Multimodal treatment for locally advanced breast cancer. Result of chemotherapy-radiotherapy versus chemotherapy-surgery. Cancer Clin Trials. 1981;44:229-36.

2. Nes JGH, Putter H, Julien JP. Preoperative chemotherapy is safe in early breast cancer, even after 10 years of follow-up; clinical and translational results from the EORTC trial 10902. Breast Cancer Res Treat. 2009;115:101-13.
3. Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy. Cancer. 2002;95:681-95.
4. Mamounas EP, Anderson SJ, Dignam JJ. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol. 2012;30(32):3960-6.
5. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. The Lancet. 2014:384(9938):164-72.
6. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol. 2008;26:778-85.
7. Keune JD, Jeffe DB, Schootman M, Hoffman A, Gillanders WE, Aft RL. Accuracy of ultrasonography and mammography in predicting pathologic response after neoadjuvant chemotherapy for breast cancer. Am J Surg. 2010;199(4):477-484.
8. Sudhir R, Koppula VC, Rao TS, Sannapareddy K, Rajappa SJ, Murthy SS. Accuracy of digital mammography, ultrasound and MRI in predicting the pathological complete response and residual tumor size of breast cancer after completion of neoadjuvant chemotherapy. Indian J Cancer. 2022;59(3):345-53.
9. LeVasseur N, Sun J, Gondara L, Diocee R, Speers C, Lohrisch C, et al. Impact of pathologic complete response on survival after neoadjuvant chemotherapy in early-stage breast cancer: a population-based analysis. J Cancer Res Clin Oncol. 2020;146(2):529-36.
10. Broglio KR, Quintana M, Foster M, Olinger M, McGlothlin A, Berry SM, et al. Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes: A Meta-Analysis. JAMA Oncol. 2016;2(6):751-60.
11. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19(1):27-39.
12. Masood S. Neoadjuvant chemotherapy in breast cancers. Women's Health. 2016;12(5):480-91.
13. Martin M. Docetaxel, doxorubicin and cyclophosphamide (the TAC regimen): an effective adjuvant treatment for operable breast cancer. Womens Health (Lond). 2006;2(4):527-37.
14. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Weaver C, et al. Breast Cancer International Research Group 001 Investigators. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005;352(22):2302-13.
15. Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MMA. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173797 patients. BMJ. 2015;351:h4901.
16. Pierga JY, Robain M, Jouve M, Asselain B, Diéras V, Beuzeboc P, et al. Response to chemotherapy is a major parameter-influencing long-term survival of metastatic breast cancer patients. Ann Oncol. 2001;12(2):231-7.

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