Predictive Value of Ki67 for Adjuvant Chemotherapy in Node-Negative, Hormone Receptor-Positive Breast Cancer

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Background: *Ki67 labeling index (Ki67 LI) is a measure of tumor proliferation. In breast cancer, evidence supporting its prognostic value is clear and its predictive value for response to treatment finds some benefits. However, studies of Ki67 LI as a predictive marker in early breast cancer are still limited worldwide and there is no data in Thailand.*
Objective: *To assess the predictive value of Ki67 expression for adjuvant chemotherapy in patients with node-negative, hormone receptor-positive breast cancer.*
Material and Method: *The authors retrospectively evaluated 127 diagnosed early breast cancer with node-negative, hormone receptor-positive patients and receiving adjuvant systemic treatment at Siriraj hospital. Disease free survival (DFS) was compared with the log-rank test according to Ki67 LI and adjuvant systemic treatment (chemoendocrine therapy and endocrine therapy alone).*
Results: *At a median follow-up of 3.3 years. The 5-year DFS rate was 79% for patients with low Ki67 expression and 75% for patients with high Ki67 expression. Of the 127 patients, 56 (44.1%) received chemoendocrine therapy and 71 (55.9%) were treated with endocrine therapy alone. There was no different effect of DFS among those receiving adjuvant endocrine therapy alone and those receiving adjuvant chemoendocrine therapy depending on Ki67 expression.*
Conclusion: *Among patients with node-negative, hormone receptor-positive breast cancer, a high Ki67 LI had worse DFS trend than a low Ki67 LI but the Ki67 LI did not predict the efficacy of adjuvant chemotherapy.*

Keywords: *Adjuvant chemotherapy, Ki67, Breast cancer*

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Breast cancer is the most common cancer diagnosed in Thai women[1]. The treatment of early breast cancer utilizes a multidisciplinary approach, including locoregional treatment with surgery with/without radiation and adjuvant systemic treatment with chemotherapy and/or hormonal therapy.

In 2009, the 11th St.Gallen international expert consensus on the primary therapy of early breast cancer recommended the inclusion of adjuvant endocrine therapy in almost all patients whose tumors present any detectable estrogen receptor[2]. The threshold for recommending chemotherapy for patients with estrogen receptor-positive disease had depended on risks of recurrence. Those included (1) Clinical features, e.g., tumor size, number of metastatic lymph nodes, histological grading and peritumoral vascular invasion; (2) Pathological features e.g. estrogen receptor (ER) and progesterone receptor (PgR) level, HER-2 status and Ki67 labeling index (Ki67 LI); (3) Gene expression by multigene assays; and (4) Patient preference[2]. The aim of adjuvant systemic treatment is to eradicate distant micrometastases which reduces the risk of recurrence and death but also has an associated risk. Therefore it would be useful to be able to select the optimal adjuvant treatment for an individual patient based on established predictive factors.

Noticeably, the group of node-negative, hormonal receptor-positive patients has good response to endocrine therapy; however, the existence of those is uncertain while some of these patients may benefit from the addition of chemotherapy to endocrine therapy. For the purpose of preventing ineffective therapies as well as unnecessary treatment-related toxicity and cost reduction, several studies have evaluated a variety of factors which may predict the relative efficacy of

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adjuvant chemoendocrine therapy compared with endocrine therapy alone.

Ki67 is a nuclear non-histone protein that is present at low levels in quiescent cells but is increased in proliferating cells, especially in the G2, M and latter half of the S phase. Ki67 LI is a measure of tumor proliferation that has been associated with breast cancer outcome in meta-analysis[3-5]. Several other studies have examined the value of using tumor Ki67 expression to predict the response of chemotherapy. Chang et al and Archer et al have suggested that a high Ki67 LI is a predictive marker of neoadjuvant chemotherapy, whereas a few small studies have found no such association[6-8]. In adjuvant setting, Yerushalmi R et al have reported that low Ki67 predicted benefit from tamoxifen in patients with ER-positive, node-negative, T1/T2 tumor for which Ki67 status was determined by immunohistochemistry using 10% cells staining as a cutoff value[9]. Viale G et al has demonstrate that a high Ki67 LI is associated with worse disease-free survival but does not predict a better response to adjuvant chemotherapy by using median valve of Ki67 LI in study (19%) as the cut point[10]. Interestingly, standard cut off point of high or low level of Ki67 LI is still unclear.

Recently, despite the 12th St. Gallen International Breast Cancer Conference 2011 expert consensus which defines less than 14% as Ki67 low level, it is derived from comparison with gene array data as a prognostic factor, while its value as a predictive factor has remained largely unclear[11,12]. The objective of this retrospective study was to examined whether the Ki67 LI at cut-point of 14% could identify patients who might particularly benefit from the addition of chemotherapy to endocrine therapy in node-negative, hormone receptor-positive breast cancer in the adjuvant setting and also to determine the prognostic value of this marker. To our knowledge this study has not yet been undertaken in Thailand, so the present study will be provide the first information.

Material and Method

The authors performed an institutional review board-approved retrospective review of Siriraj Hospital medical database and pathological database, to identify patients with the diagnosis of early breast cancer between 2001 and 2008; the principal eligibility criteria for this study included patients with hormonal receptor-positive, node-negative disease. Patients with incomplete medical database or pathological database were excluded from study. The data of adjuvant endocrine and chemotherapy therapy, disease recurrence and death were collected.

Pathological review

A tumor block of patients with early breast cancer was obtained from the pathology department, Siriraj Hospital, with approvals from Ethics committees. The tissues were documented by routine pathological examination. Tumor size, histological subtype, histological grade, number of metastatic lymph node and lymphovascular invasion were documented. Immunohistochemistry for ER, PgR and HER-2 status were also determined.

For patients with node-negative, hormone receptor-positive breast cancer, immunohistochemistry for Ki67 LI was assessed using mouse monoclonal antibody MIB-1 (1:200 dilution; Dako); the percentage of cells that showed definite nuclear immunoreactivity with MIB-1 was recorded.

ER and PgR status were classified as present (more than or equal to 1% immunoreactive cells) or absent (less than 1% immunoreactive cells). HER-2 status was considered to be positive if the staining intensity score was 3+ or FISH/CISH positive, negative if the staining intensity score was 0, 1+ and equivocal if the staining intensity score 2+. The Ki67 LI was determined semiquantitatively as high (more than or equal to 14% immunoreactive cells) and low (less than 14% immunopositivity), respectively.

Statistical methods

The primary trial end point was disease free survival (DFS), defined as the time from the diagnosis to the earliest time of invasive recurrence or death from any cause; in the absence of recurrence or death, patients were censored at the date of the last follow-up.

The Chi-square test was used to determine significant differences in patient characteristics according to Ki67 LI level. The distribution of DFS was estimated using the Kaplan-Meier product limit method according to Ki67 LI status (high versus low) in the overall population. The log-rank test was used to compare DFS between groups and compare chemoendocrine therapy versus endocrine therapy alone. The p-value less than 0.05 as statistically significant. The analysis was performed using the statistical software SPSS for Windows, version 13.

Results

Patient characteristics

Demographic and disease characteristics of

127 patients evaluated in this analysis are reported in Table 1. The median age of overall patients was 55 years (range 27-87 years). As previously stated, all patients were node-negative and had hormonal receptor-positive disease. Ki67 LI was high level (more than or equal to 14%) in 51 patients (40.2%) and low level (less than 14%) in 76 patients (59.8%). As expected, high level Ki67 LI were more likely to be high grade and HER-2 status positive. The percentage of patients with high level Ki67 LI had grade 3 was 25.5% vs. 14.5% which contrasted with the percentage of patients with low level Ki67 LI had grade 1 which was 27.6% vs. 9.8%. It was a statistical significance: p = 0.031. While we also found a higher percentage of patients with high level Ki67 LI had HER-2 status positive by immunohistochemistry (27.5% vs. 13.2%) but it was not of statistical significance. No statistically significant difference in tumor size, peritumoral vascular invasion and PgR status was found.

Fifty-six patients (44.1%) received adjuvant systemic chemotherapy, 47 (37%) were treated with adriamycin and cyclophosphamide regimen, 7 (5.5%) were treated with cyclophosphamide, methotrexate and fluorouracil regimen. All patients received adjuvant systemic endocrine therapy for breast cancer (Table 2).

Prognostic value of Ki67 LI in the overall population and in the recurrence group

The median follow-up for all patients was 3.3 years (range 0.09 to 7.59 years). At data cutoff (November 2011), 22 patients (17.32%) had disease recurrence, 6 patients were locoregional recurrence, 9 patients were distant metastasis and 3 were both locoregional and distant metastasis. For those with disease recurrence, one patient had died from disease progression. The 3-year DFS rate was 88% for patients with low Ki67 expression and 81% for patients with high Ki67 expression. The 5-year DFS rate was 79% for patients with low Ki67 expression and 75% for patients with high Ki67 expression. However, the authors still

Table 1. Patient characteristics stratified by Ki-67 labeling index

Characteristics	Overall	Ki67 LI more than or equal to 14%	Ki67 LI less than 14%	p-value
All patients, n	127	51	76	-
Mean age, years (range)	55 (27-87)	53 (27-87)	56 (31-85)	0.674
Median follow-up, years (range)	3.3 (0.09-7.59)	3.4 (2.04-7.59)	3.06 (0.09-7.54)	-
Tumor size, n (%)				0.467
2 cm or less	63 (49.6)	27 (52.9)	36 (47.4)	
> 2 to 5 cm	59 (46.5)	21 (41.2)	38 (50)	
More than or equal to5 cm	5 (3.9)	3 (5.9)	2 (2.6)	
Tumor grade, n (%)				0.031*
Grade 1	26 (20.5)	5 (9.8)	21 (27.6)	
Grade 2	77 (60.6)	33 (64.7)	44 (57.9)	
Grade 3	24 (18.9)	13 (25.5)	11 (14.5)	
Peritumoral vascular invasion, n (%)				0.313
Not present	107 (84.3)	45 (88.2)	62 (81.6)	
Present	20 (15.7)	6 (11.8)	14 (18.4)	
Mean ER, %	68.5	68.5	68.6	-
Mean PgR, %	50.3	49.3	51	-
PgR status, n (%)				0.584
Absent	15 (11.8)	7 (13.7)	8 (10.5)	
Present	112 (88.2)	44 (86.3)	68 (89.5)	
HER2 status by IHC, n (%)				0.128
Negative (0,1+)	91 (71.6)	33 (64.7)	58 (76.3)	
Eguivocal (2+)	12 (9.4)	4 (7.8)	8 (10.5)	
Positive (3+)	24 (18.9)	14 (27.5)	10 (13.2)	

Abbreviations: Ki67 LI, Ki67 labeling index; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry staining. * Statistical significant value

have not found a remarkable correlation between Ki67 LI and DFS of all patients (log-rank p = 0.398; Fig. 1). The median DFS had not yet been reached for both high and low Ki67 expression groups.

Furthermore, according to Ki67 LI in the recurrence group, the proportions of patients who had disease recurrence in low level Ki67 LI and high level Ki67 LI were 12 (15.8%) of 76 and 10 (19.6%) of 51, respectively. the median DFS was 2.69 years (95% CI = 1.85-3.52) for patients with low Ki67 expression and 2.56 years (95% CI = 1.90-3.23) for those with high Ki67 expression (log-rank p = 0.361; Fig. 2).

Predictive value of Ki67 LI

Of the 127 patients with node-negative, hormone receptor-positive breast cancer who were treated with adjuvant systemic therapy, 56 (44.1%) received chemoendocrine therapy and 71 (55.9%) were treated with endocrine therapy alone. The proportions of patients who had disease recurrence in each group were 9 (16%) of 56 and 13 (18.3%) of 71 at the time of this analysis.

The authors explore a predictive value of Ki67 LI, comparing chemoendocrine therapy versus endocrine therapy alone in patients with low or high Ki67 LI. There was no different effect of DFS between adjuvant endocrine therapy alone and adjuvant chemoendocrine therapy depending on low and high Ki67 expression (median survival was not reached for both groups, Log-rank p = 0.519 and p = 0.599, respectively; Fig. 3).

Discussion

Among patients with node-negative, hormone receptor-positive breast cancer, the 21-gene Oncotype DX recurrence score has demonstrated value as

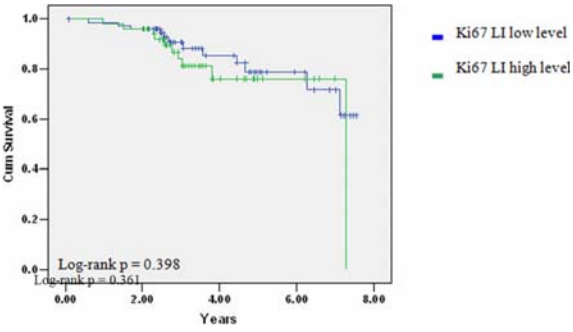

Fig. 1 Estimated disease free survival according to Ki67 LI (high level Ki67 LI vs. low level Ki67 LI) in the overall population (n = 127)

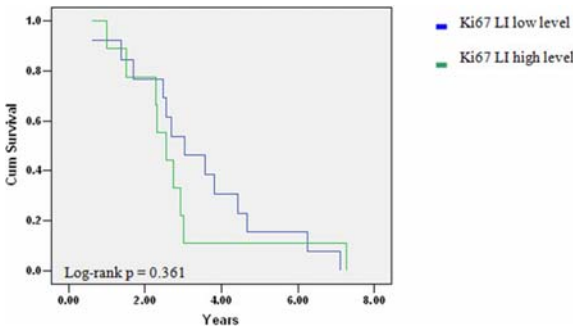

Fig. 2 Estimated disease free survival according to Ki67 LI (high level Ki67 LI vs. low level Ki67 LI) in therecurrence group (n = 22)

Table 2. Adjuvant systemic therapy administered

Adjuvant systemic therapy	Overall	Ki67 LI more than or equal to 14%	Ki67 LI less than 14%
Type of chemotherapy, n (%)			
AC regimen	47 (37)	27 (52.9)	20 (26.3)
CMF regimen	7 (5.5)	2 (3.9)	5 (6.6)
FAC regimen	1 (0.8)	0	1 (1.3)
Others (*e.g.* TC)	1 (0.8)	0	1 (1.3)
No adjuvant chemotherapy	71 (55.9)	22 (43.2)	49 (64.5)
Type of endocrine, n (%)			
Tamoxifen monotherapy	99 (78)	42 (82.4)	57 (79)
AI monotherapy	19 (15)	7 (13.7)	12 (15.8)
Switching AI	7 (5.5)	1 (2.0)	6 (7.9)
Extended AI	2 (1.6)	1 (2.0)	1 (1.3)

Abbreviations: Ki67 LI, Ki67 labeling index; AC, adriamycin + cyclophosphamide; CMF, cyclophosphamide + methotrex ate + fluorouracil; FAC, fluorouracil + adriamycin + cyclophosphamide; AI, aromatase inhibitor

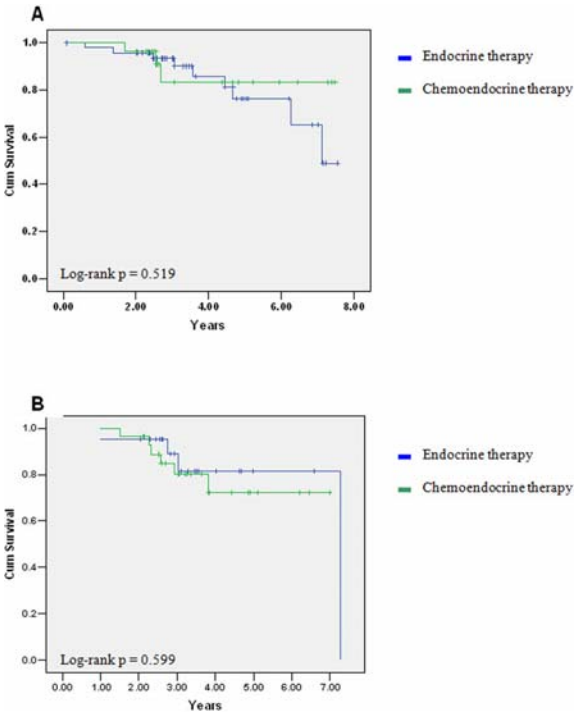

Fig. 3 Estimated disease free survival for patients with (A) low level Ki67 LI (less than 14%) and (B) high level Ki67 LI (more than or equal to 14%) who received adjuvant endocrine therapy alone versus chemoendocrine therapy

predictive parameter for the efficacy of adjuvant chemotherapy[13]. But the cost of this test is too high when concern about cost-benefit in developing countries. Many studies have sought other effective and lower cost predictive markers. Noticeable, Ki67 is a mainly part of gene associated with cell proliferation in those available predictive tools, so it is hypothesized to be a predictive marker for role of adjuvant chemotherapy in patients with hormone receptor-positive breast cancer. However, there are very few studies and conflicting results e.g. Llorca FP et al reported that Ki67 is a biomarker candidate for predicting docetaxel efficacy in node-positive, estrogen receptor-positive breast cancer[14]. But contradictly, Viale G et al reported that Ki67 expression was not predictive for cyclophospamide, methotrexate, and fluorouracil efficacy in node-negative, endocrine responsive breast cancer[10].

The present study was a retrospective study to evaluate the predictive value of Ki67 for adjuvant chemotherapy in node-negative and hormone receptor-positive breast cancer. As expected, this result found correlation of Ki67 LI with histological grade, which has been described previously in the 12th St. Gallen International Breast Cancer Conference 2011 expert consensus. As well, this result also showed that patients with high Ki67 expression had worse 3-year and 5-year DFS rate than those with low expression but our study still found no statistical significance and Ki67 LI did not predict the better outcome to adjuvant chemotherapy.

Concerning the presence of HER-2 over expression which is associated with increased tumor aggressiveness, increased rates of recurrence and increased mortality, adjuvant treatment of early-stage breast cancer with combined trastuzumab and chemotherapy has both benefited and become the standard treatment in patients with HER2-positive node negative and positive tumors[15]. Notably, the present study has some populations of Her-2 positive and equivocal status (13.2% and 10.5%, respectively) as in the low level Ki67 group. All those with HER2-positive tumors had a tumor size > 1 cm. This may be a possible reason for no significant difference in survival benefit of chemotherapy, according to low and high Ki67 expression only.

Previous studies (e.g. Yerushalmi R et al) examined the predictive value of Ki67 LI to predict benefit from tamoxifen in 710 patients; median follow-up was 12.4 years; Viale G et al studied the predictive value of Ki67 LI to predict benefit from adjuvant chemotherapy in 758 patients with premenopausal status and 1,166 patients with postmenopausal status; median follow-up for each group was 10 years (Table3). In our study, only 127 patients with the median follow-up of 3.3 years were assessed. The median survival was still not reached for either group. Thus the present study has not yet enough events or long enough follow-up to detect a difference in survival.

Ki67 may be the good predictive marker for the noting benefit of adjuvant chemotherapy. However, our study did not confirm that; this may be due to small sample sizes and short follow-up. Nevertheless, to our knowledge, this is the first study exploring the role of Ki67 LI as a predictive marker for adjuvant systemic treatment in patients with node-negative, hormone receptor-positive breast cancer in Thailand.

Conclusion

Among early breast cancer with node-negative, hormone receptor-positive patients and receiving adjuvant systemic treatment, a high Ki67 LI had worse DFS trend than a low Ki67 LI, but the Ki67 LI did not predict the efficacy of adjuvant chemotherapy.

Table 3. Previous studies of proliferative index Ki67 as a predictive marker for adjuvant treatment in early breast cancer patients with hormone-receptor positive

Study	Number of patients	Ki67 Cutoff value	Treatment	Median follow (yr)	p-value
Yerushalmi R et al[9]	710	10%	tamoxifen vs. no tamoxifen	12.4	0.01
Viale G et al[10]	758 from IBCSG trials VIII (premenopausal status)	19%	CMF → tamoxifen vs. tamoxifen	10	0.90
	1,166 from IBCSG trials IX (postmenopausal status)	19%	CMF → Goserelin vs. CMF vs. Goserelin	10	0.45
Llorca FP et al[14]	798 from PACS01 (node positive)	20%	FEC vs. FEC → D	4.9	0.046

Abbreviations: CMF, cyclophosphamide + methotrexate + fluorouracil; FEC, fluorouracil + epirubicin + cyclophosphamide; D, docetaxel; NS, not statistically significant

Potential conflicts of interest

None.

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การใช้ Ki67 เป็นตัวทำนายผลการรักษาเสริมเคมีบำบัด ในผู้ป่วยมะเร็งเต้านม ที่โรคยังไม่แพร่กระจายไปต่อมน้ำเหลืองและมีตัวรับต่อฮอร์โมนเป็นผลบวก

อภิษฎา สุเทพวานนท์, มาลี วรรณิสสร, วิเชียร ศรีมุนินทร์นิมิต

***ภูมิหลัง**: ค่า Ki67 เป็นตัวหนึ่งที่ใช้บ่งถึงการแบ่งตัวของเซลล์มะเร็ง มีหลายการศึกษาในผู้ป่วยมะเร็งเต้านมสนับสนุนว่าค่า Ki67 เป็นตัวพยากรณ์โรคตัวหนึ่ง และมีบางการศึกษาย้อนหลังที่พบว่าสามารถใช้ทำนายผล การรักษาว่าจะได้ประโยชน์หรือไม่ อย่างไรก็ตามการศึกษาดูความสัมพันธ์ของค่า Ki67 กับมะเร็งเต้านมในการเป็นตัวทำนายผลการรักษายังไม่เคยมีการศึกษาในประชากรไทยมาก่อน*

***วัตถุประสงค์**: เพื่อศึกษาความสัมพันธ์ของค่า Ki67 ในการทำนายผลจากการรักษาเสริมเคมีบำบัด ในกลุ่มผู้ป่วยมะเร็งเต้านมที่โรคยังไม่แพร่กระจายไปต่อมน้ำเหลืองและมีตัวรับต่อฮอร์โมนเอสโตรเจน*

***วัสดุและวิธีการ**: ศึกษาในผู้ป่วยมะเร็งเต้านมที่โรคยังไม่แพร่กระจายไปต่อมน้ำเหลืองและมีตัวรับต่อฮอร์โมนเอสโตรเจน 127 ราย ซึ่งเข้ารับการรักษาเสริมหลังผ่าตัดที่โรงพยาบาลศิริราช โดยศึกษาดูความสัมพันธ์ ระหว่างค่า Ki67 กับ อัตราการปลอดจากการกลับมาของมะเร็งในช่วง 5 ปี ในกลุ่มที่ได้รับการรักษาเคมีบำบัด ร่วมกับฮอร์โมนและกลุ่มที่ได้รับการรักษาฮอร์โมนเพียงอย่างเดียว*

***ผลการศึกษา**: ณ ระยะเวลาติดตามผู้ป่วยเฉลี่ย 3.3 ปี อัตราการปลอดจากการกลับมาของมะเร็งในช่วง 5 ปี ของกลุ่มที่ค่า Ki67 ต่ำ คือ 79% และกลุ่มที่ค่า Ki67 สูง คือ 75% การรักษาเสริมหลังการผ่าตัด มีผู้ป่วย 56 ราย (44.1%) ได้รับการรักษาเคมีบำบัดร่วมกับฮอร์โมน และมีผู้ป่วย 71 ราย (55.9%) ได้รับการรักษาฮอร์โมนเพียงอย่างเดียว ซึ่งอัตราการปลอดจากการกลับมาของมะเร็งในช่วง 5 ปีในกลุ่มที่ได้รับการรักษา เคมีบำบัดร่วมกับฮอร์โมนและกลุ่มที่ได้รับการรักษาฮอร์โมนเพียงอย่างเดียว ไม่ได้มีความสัมพันธ์กับค่า Ki67*

***สรุป**: ในผู้ป่วยมะเร็งเต้านมที่โรคยังไม่แพร่กระจายไปต่อมน้ำเหลืองและมีตัวรับต่อฮอร์โมนเอสโตรเจน การตรวจพบค่า Ki67 ที่สูง จะมีแนวโน้มในการที่โรคจะกลับเป็นซ้ำและมีการพยากรณ์โรคที่ไม่ดีเมื่อเทียบกับ ค่า Ki67 ที่ต่ำ แต่อย่างไรก็ตาม ค่า Ki67 ที่สูงไม่สามารถใช้ทำนายผลการรักษาว่าจะได้ประโยชน์ จากการรักษาเสริมด้วยเคมีบำบัด*