A Phase II Study of the Combination of Gemcitabine Plus Carboplatin as the Neoadjuvant Treatment in Locally Advanced Breast Cancer

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Objective: *Although anthracycline-based regimen is standard neoadjuvant chemotherapy (NAC) for locally advanced breast cancer (LABC), there is some concern over its toxicities such as alopecia and cardiotoxicity. Gemcitabine is another active agent in metastatic breast cancer after failure to anthracycline with less toxicity. The objective of the present study is to evaluate the efficacy and safety of the combination of gemcitabine and carboplatin as NAC in LABC.*

Material and Method: *Patients with histologically confirmed LABC (T3, T4 or N2 and M0) were included. Patients were scheduled to receive 3 cycles of neoadjuvant GC (gemcitabine 1,000 mg/m^2 D1, D8 and carboplatin AUCx5 D1) every 21 days. Patients with clinical response underwent surgery and additional 3 cycles of adjuvant GC. Primary end point was clinical response rate whereas secondary end points included pathological response, DFS, OS and toxicity.*

Results: *Between 2004 and 2007, 40 LABC patients were enrolled. Of 40 patients, 35 were evaluable for efficacy and 40 for toxicity. Twenty-three out of 35 patients (65%) obtained cPR. Among 22 patients who had clinical response and who underwent surgery, overall pathological response rate was 51.5% with 1-pCR (2.9%) and 17-pPR (48.5%). All 7 triple-negative patients had pathological response (1-pCR, 6-pPR). At median follow-up of 59 months, median DFS and OS were not reached. Five-year OS and DFS were 67% and 62%, respectively. Major adverse effect was myelosuppression without fatal complications.*

Conclusion: *The combination GC was feasible and well-tolerated for LABC in neoadjuvant setting. Triple-negative subgroup seems to have high response to GC.*

Keywords: *Carboplatin, Chemotherapy, Gemcitabine, Locally advanced breast cancer, Neoadjuvant therapy*

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Breast cancer is the most common malignancy in the Thai female. Patients were often diagnosed with locally advanced disease. Neoadjuvant chemotherapy (NAC) has been used as the initial treatment in locally advanced breast cancer (LABC), followed by definite surgery. Neoadjuvant chemotherapy offers some benefits in which the primary tumor can be used as in vivo assessment of the treatment response to modify subsequent patient treatment, with additional hope of down-staging and avoidance of mastectomy. Also, NAC is an ideal tool to assess and predict clinical and pathological responses which are predictor of survival. Current data indicate that the pathological complete response (pCR) may be a surrogate indicator for benefit of NAC in terms of disease-free and overall survival[1-3]. Randomized trials demonstrated equivalent benefits of neoadjuvant and adjuvant chemotherapy in operable breast cancer[3,4].

Standard chemotherapy as neoadjuvant and adjuvant treatment for breast cancer is anthracycline

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containing regimens such as doxorubicin plus cyclophosphamide (AC) or 5-Fluorouracil, doxorubicin plus cyclophosphamide (FAC). Response rate ranges from 65 to 80 percent[3-6]. Although doxorubicin is the most active agent in breast cancer, it has some undesirable toxicities such as moderate nausea and vomiting, alopecia, cardiotoxicity and skin necrosis if extravasation occurs.

Gemcitabine has demonstrated clinical antitumor activity in breast cancer. Response rates of 20 to 30 percent have been observed in patients with anthracycline pretreated metastatic breast cancer[7,8]. The combination of gemcitabine with cisplatin has demonstrated a response rate of 40 percent in pretreated metastatic breast cancer patients[9]. However, cisplatin has some unfavorable toxicities such as severe nausea, vomiting, nephrotoxicity and neurotoxicity. Carboplatin, with less toxicity compared to cisplatin, has demonstrated response rates of 25-37 percent in chemotherapy-naive metastatic breast cancer patients[10,11]. The authors hypothesized that the combination of carboplatin plus gemcitabine are as effective as combination of cisplatin and gemcitabine with less toxicity and can be administered in the outpatient care setting.

The purpose of the present study is to evaluate the efficacy and safety of the combination of gemcitabine with carboplatin (GC) as induction chemotherapy in patients with LABC. The results of the present study may be useful and provide a preliminary result for establishing a new well-tolerated standard chemotherapy regimen as NAC for LABC.

Material and Method

Patients

Patients with pathologically confirmed LABC (T3, T4 or any T with N2, M0 lesion) were candidates for inclusion in the present study. The eligible patients were required to be between 18 and 60 years of age with ECOG performance status of 0-1. All eligible patients were required to have bidimensional measurable lesion with adequate bone marrow function as indicated by neutrophil and platelet value being higher than 1,500/mm^3 and 100,000/mm^3, respectively. The eligible patients must have adequate renal function (serum creatinine less than 1.5 mg/dL) and liver function (serum bilirubin and liver transaminase less than 2 times of upper normal limit).

The patients with inflammatory breast cancer or documented distant metastasis including ipsilateral supraclavicular lymph node involvement were excluded. Those with other active primary tumor except basal and squamous cell carcinoma of skin or those with any conditions which prevent adequate follow-up were ineligible. All patients provided written consent prior to their inclusion in the present study. The present study was approved by Siriraj Institutional Review Board.

Definitions

Staging was defined according to the criteria determined by American Joint Committee (AJCC) 6th version, Tumor size was measured using ultrasonography at baseline and after completion of neoadjuvant GC, the two greatest perpendicular diameters of tumors were measured and the product of these diameters were added as a measure of total tumor size. Clinical complete response (cCR) was defined when there was no clinical evidence of tumor in breast and axillary lymph nodes. Reduction of the tumor size of 50% or greater without new lesions was graded as clinical partial response (cPR). Clinical progressive disease (cPD) was defined as any increase greater than 25 percent of tumor size or appearance of new lesion. The tumor that did not meet the criteria of cCR, cPR or cPD was considered to be clinical stable disease (cSD). This classification was also used for defining the pathological response. At surgery, no invasive cancer in breast and axillary lymph nodes were considered pathological complete response (pCR).

Overall survival (OS) was estimated from date of enrollment to date of death from any cause. Disease-free survival (DFS) was calculated from start of study to the first evidence of recurrence.

The toxicities were reported according to standard criteria for assessment of therapy induced toxicity of National Cancer Institute (NCI), version 3.

Methods

Eligible patients were scheduled to receive three cycles of neoadjuvant GC. Each cycle consisted of carboplatin dosage of AUCx5 on day 1 plus gemcitabine 1,000 mg/m^2 on day 1 and day 8. The cycle was repeated at three-week interval. Following the induction period, clinical responses were assessed clinically and radiolographically by mammography or ultrasonography of breast. Within 4 weeks after the third cycle, patients with cPR or cCR were pursued for surgical tumor removal with either modified radical mastectomy or lumpectomy with axillary lymph node dissection upon the discretions of the surgeons. Those with cSD or cPD were taken off the study and received

standard anthracycline-based regimen. The scheme of management is shown in Fig. 1.

Pathological assessments were performed and reported as having pathological response using the same definitions as clinical response. Two to four weeks after surgery, adjuvant treatment was considered based on the pathological results. The patients with pCR or pPR received additional three cycles of GC as adjuvant treatment. The adjuvant chemotherapy was altered to standard anthracycline-based regimen in non-responders (pPD or pSD). All patients were scheduled to receive adjuvant radiation at the chest wall and involved area. Hormonal treatments were prescribed for hormone positive breast cancer patients for 5 years.

The patients who followed at the first visit approximately 30 days after the last dose of study drugs were administered and then every 3 months during the first 2 years, every 6 months in the next 3 years and then once a year until disease progression. The follow-up schedules included liver function test and chest x-ray each follow-up and yearly mammography. Other investigations such as ultrasound of liver and bone scan were repeated as indicated only when abnormal physical exam or blood chemistry was found.

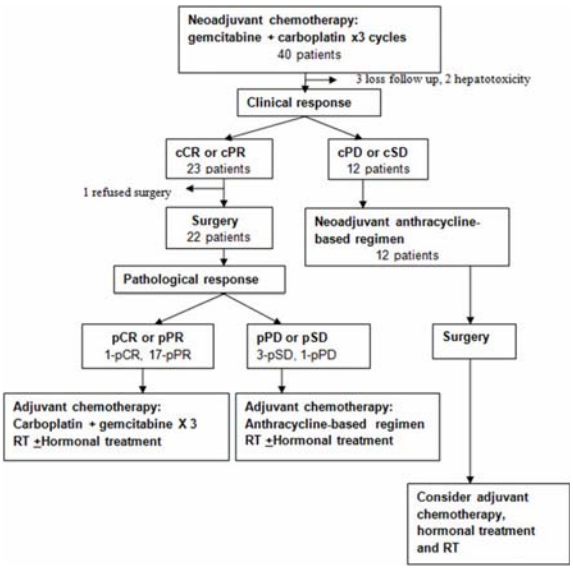

Fig. 1 Study design and scheme of study. Forty locally advanced breast cancer patients were initially enrolled. Thirty-five patients were eligible for clinical response assessment. Of these 35 patients, 23 had clinical partial response and 22 patients were evaluated for pathological response from GC after surgery. Twelve patients with no clinical response from GC were given anthracycline-based chemotherapy

Statistical analysis

The primary outcome of the present study was clinical response rate of GC as induction chemotherapy in LABC. The secondary outcomes included pCR rate, DFS, OS as well as toxicities.

Baseline characteristics, response rate and adverse events were presented in terms of percentages, median, or mean with standard deviation. Survival analyses were conducted using Kaplan Meier method. In the absence of death or progressive disease, follow-up was censored at last contact. Log-rank test and Cox-proportional hazards models were used to compare survival between subgroups. All statistical analyses were performed using computer software (SPSS version 13). Analyses of end data reported here are based on information received as on January 31, 2012 with the median follow-up time of 59 months.

Results

Patients' characteristics and treatments

Between July 2004 and July 2007, forty female patients were enrolled in the present study according to inclusion criteria described above. The age ranged from 26 years to 65 years, with the median age of 46 years old. About two-third of patients were premenopausal. For the clinical stage, more than half of our patients were diagnosed of stage IIIB. Twenty-three patients (57.5%) presented with breast mass with skin or chest wall involvement (T4). Estrogen and/or progesterone receptor were positive in 14 patients (35%). Seven patients (17.5%) had triple-negative breast cancer. Patient's characteristics are shown in Table 1.

Of 40 patients, 35 patients (87.5%) who completed 3 cycles of planned neoadjuvant GC were evaluable for efficacy. Two patients discontinued scheduled GC because of their preference after having asymptomatic grade 3 hepatotoxicity. One of these 2 patients had cPR following 2 cycles of GC and proceeded to surgical treatment (modified radical mastectomy). Three patients refused further treatment and were lost to follow-up after receiving 1 cycle of GC. Following adjuvant chemotherapy, adjuvant radiation was given to 31 patients (77.5%) and adjuvant hormonal treatment intended for 5 years was offered to all patients with positive hormonal receptor. Eleven patients received tamoxifen and 3 patients received aromatase inhibitor as initial hormonal treatment.

Clinical and pathological response

Of the 35 patients who completed neoadjuvant GC, 23 (65.7%) achieved cPR by clinical assessment. Among the 22 patients who achieved cPR from GC and received surgery, there were 1 patient with pCR and 17 patients with confirmed pPR. These patients (18 patients) then received additional 3 cycles of adjuvant GC. Adjuvant anthracycline-based regimens (AC or FAC) were considered in another 4 patients with pPD or pSD after neoadjuvant GC. Clinical and pathological response rates are summarized in Table 2.

There were 11 patients who achieved cSD whereas there was 1 patient who had cPD after neoadjuvant GC. The administration of all of these patients were changed to receiving preoperatively additional 3 cycles of doxorubicin and cyclophosphamide (AC) because of inadequate response to GC. Although these patients had previous inadequate response from first-line GC, 11 out of those 12 patients had dramatic response to subsequent AC (1-cCR and 10 cPR). Unfortunately, one patient, who developed cCR following neoadjuvant AC, refused further surgical treatment and was lost to follow-up. Ten out of 11 patients with cPR from AC were proved to have pPR. Another patient was proved to have cSD after receiving 3 cycles of AC.

Disease free survival and overall survival

At median follow-up of 59 months, 19 patients (47.5%) were alive with disease-free, 2 patients (5%) were alive with disease progression and 14 patients (35%) were dead. The median OS and DFS were not reached. Five-year DFS and OS were 62 and 67 percent, respectively. Sixteen patients (40%) were relapsed or developed disease progression. There was no difference in terms of DFS and OS between patients who had PR or CR from GC and non-responders.

Outcome in patients with triple-negative breast cancer

Seven out of 40 patients were classified as triple-negative breast cancer patients. Interestingly, all of these patients had clinical and pathological response after receiving neoadjuvant GC (1-pCR, 6-pPR). Mean DFS in triple-negative patients was 68.9 months (95% CI: 47.8-90 months) which was not significantly different to other subtypes (mean DFS of 54.7 months (95% CI: 42.4-67.1 months), p = 0.54). There was no difference in terms of overall survival in these particular patients either (mean OS of 78.2 months in triple-negative patients whereas it was 62.5 months in other patients, p = 0.22).

Table 1. Characteristics of eligible patients

Patients' characteristics	Number of patients (%)
Gender	
Female	40 (100)
Age, years	
median (range)	46 (26-65)
mean (SD)	47.1 (9.2)
Menopausal status	
Premenopausal	25 (62.5)
Postmenopausal	15 (37.5)
Primary tumor	
T2	1 (2.5)
T3	16 (40)
T4	23 (57.5)
Clinical nodal status	
N0	18 (45)
N1	13 (32.5)
N2	9 (22.5)
Cilinical stage	
IIB	9 (22.5)
IIIA	8 (20)
IIIB	23 (57.5)
Hormonal receptor	
Positive ER and/or PR	14 (35)
Negative ER and PR	21 (52.5)
Unknown	5 (12.5)
HER2 receptor	
Positive 3+	9 (22.5)
Positive 2+	7 (17.5)
Negative	18 (45)

Table 2. Clinical and pathological response

Response	Number of patients (%)
Clinical response (n = 35[+])	
Complete response (cCR)	0 (0)
Partial response (cPR)	23 (65.7)
Stable disease (cSD)	11 (31.4)
Progressive disease (cPD)	1 (2.9)
Pathological response (n = 35)	
Complete response (pCR)	1 (2.9)
Partial response (pPR)	17 (48.6)
Stable disease (pSD)	3 (8.5)
Progressive disease (pPD)	1 (2.9)
Undetermine[++]	13 (37.1)

[+] excluded 5 patients who did not finish 3 cycles of neoadjuvant GC

[++] Twelve patients received anthracycline-based regimen before surgery and one patient refused surgery

Toxicities

The combination of GC was well-tolerated with occasional grade III and IV toxicities. All patients who experienced grade III and IV toxicities did not have serious complications and most of them required no specific treatment. The major toxicity was myelosuppression with 4 patients with febrile neutropenia which improved after oral antibiotic treatment and out-patient care. Four patients (10%) developed grade III asymptomatic hepatitis and improved spontaneously after supportive treatments. The toxicity of GC is demonstrated in Table 3.

Discussion

Neoadjuvant chemotherapy has been shown to have benefit in down-staging breast cancer, increase possibility of breast conserving surgery, as well as permitting in situ assessment of chemotherapy sensitivity[12]. Standard NAC for invasive breast cancer is anthracycline-based chemotherapy with the pCR rate of 12.9% and which increased up to 26% with the addition of taxane[13]. Several studies explored the activity of gemcitabine in metastatic breast cancer. There was a substantial response to gemcitabine, even in patients who received pretreated anthracycline[7,8].

Table 3. Overall toxicity of GC regimen

Toxicities	Number of patients (%)	
	All grades	Grade 3 and 4
Anemia	35 (87.5)	18 (45)
Leukopenia	32 (80)	7 (17.5)
Neutropenia	34 (85)	27 (67.5)
Thrombocytopenia	32 (80)	15 (37.5)
Febrile neutropenia	4 (10)	0 (0)
Rash	19 (47.5)	1 (2.5)
Nausea	34 (85)	1 (2.5)
Vomiting	25 (62.5)	2 (5)
Anorexia	28 (70)	1 (2.5)
Myalgia	10 (25)	0 (0)
Arthralgia	2 (5)	0 (0)
Paresthesia	5 (12.5)	0 (0)
Fatigue	34 (85)	1 (2.5)
Mucositis	6 (15)	0 (0)
Diarrhea	3 (7.5)	1 (2.5)
Constipation	11 (27.5)	0 (0)
Renal impairment	1 (2.5)	0 (0)
Alopecia	29 (72.5)	0 (0)
Hepatitis	28 (70)	4 (10)
Allergy	2 (5)	0 (0)
Others	16 (40)	0 (0)

Considering the good tolerability and low-profile adverse effects of gemcitabine, the authors hypothesized that using gemcitabine plus carboplatin might have comparable efficacy to standard treatment but with less toxicity.

According to the present study, two-thirds of locally advanced breast cancer patients developed partial response following 3 cycles of GC with one patient with pCR (2.9%). Compared to previous studies, GC seems to provide a smaller proportion of pathological complete response. This may be because our study enrolled more advanced cancer, i.e. higher proportion of T3 and T4 lesions, when compared to other studies. However, GC was able to stabilize disease in almost all patients with rare progressive disease. It was positive to find that patients who did not have adequate response from GC, eventually had tumor shrinkage from subsequent antracycline-based chemotherapy. On the other hand, the patients who did not initially respond to GC were unnecessarily exposed to GC. These patients might have been well with anthracycline-based chemotherapy from the beginning. Although our study enrolled patients with higher stage breast cancer, 5-year DFS in our study was 62% which was comparable with the patients who received anthracycline-based NAC in the NSABP-B27 (5-year DFS 67%)[13]. Nevertheless, survival outcomes in our study were analyzed by intention to treat basis, which might not represent the effect of GC only, but were interfered with the patients who ultimately received anthracycline-based regimen.

Several phase II studies assessed the efficacy of gemcitabine-based regimen in neoadjuvant setting for breast cancer patients. Most of these studies explored the benefit of adding gemcitabine to standard anthracycline and taxane-based chemotherapy and demonstrated pCR rate of 18-23%[14-19]. Recently, Julka PK et al reported efficacy of neoadjuvant gemcitabine plus epirubicin followed by gemcitabine plus cisplatin in LABC patients[17,20]. The present study showed pCR and clinical response rate of 20 and 82 percent, respectively. Compared with the present study, the authors' lower response rate may be because of the shorter duration of chemotherapy before assessment and higher stage of cancer in overall population. However, it was found that DFS was similar (5-year DFS 62% in our study versus 4-year DFS of 63% reported previously) with much lower toxicity profiles. The comparison of the present study and previous neoadjuvant gemcitabine trials for operable/LABC patients are shown in Table 4.

Table 4. Comparison of neoadjuvant gemcitabine-based regimen for locally advanced breast cancer

Studies	Chemotherapy regimen	Number of patients	pCR[+] (%)	DFS and OS[++]
Gomez et al[16]	Gemcitabine/doxorubicin	39	18	
Hamm et al[15]	Gemcitabine/epirubicin/paclitaxel	76	23	
Julka et al[17,20]	Gemcitabine/doxorubicin followed by gemcitabine/cisplatin	65	20	4-year DFS 63%
Yardley et al[18]	Gemcitabine/epirubicin/docetaxel	110	19	Median TTP[+++] -36 months
Yardley et al[19]	Gemcitabine/epirubicin/paclitaxel (dose dense)	123	20	3-year DFS 48% 3-year OS 86%
Our study	Gemcitabine/carboplatin	40	2.9	5-year DFS 62% 5-year OS 67%

[+] pathological complete response
[++] disease free survival and overall survival
[+++] Time to treatment failure

Interestingly, all patients (7/7) who had triple-negative breast cancer did have substantial response to GC. These patients, however, had no difference in terms of OS and DFS compared to other subtypes. The dramatic response of GC in triple negative patients in the present study supports the previous study which determined that platinum has substantial activity in triple-negative breast cancer[21-24]. However, the pCR rate of patients with triple-negative breast cancer in our study (14%) was trivially lower than previous data using anthracycline-based regimen (20%)[25]. The possible reason was that the present study included patients with more advanced stage of disease with assuming poorer biology of tumors. The activity of GC regimen needs to be evaluated in a much larger study restricted to triple-negative breast cancer patients only.

The GC regimen had lower profile of toxicities such as hematotoxicity and hepatotoxicity, which resolved without requiring specific treatment. Compared to anthracycline-based chemotherapy, out patients developed much less hair loss and no report of cardiotoxicity, the most undesirable side effects of anthracycline.

Conclusion

Neoadjuvant GC in patients with LABC was found to be well-tolerated but was not superior to standard anthracycline-based chemotherapy. The result was more positive with the subgroup of triple negative breast cancer patients showing high response rate to GC. Future randomized study of neoadjuvant GC compared with standard chemotherapy for LABC is needed, especially in the subgroup of triple-negative breast cancer.

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Potential conflicts of interest

None.

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การศึกษาประสิทธิภาพของยา gemcitabine ร่วมกับ carboplatin ในการรักษานำหน้าการผ่าตัดในผู้ป่วยโรคมะเร็งเต้านมระยะลุกลามเฉพาะที่ (locally advanced breast cancer)

ศุทธินี อิทธิเมฆินทร์, อดุลย์ รัตนวิจิตราศิลป์, วุฒิศิริ วีรสาร, จารุวรรณ เอกวัลลภ, นพดล โสภารัตนาไพศาล, ศุภกร โรจนนินทร์, พรชัย โอเจริญรัตน์, ปรมาภรณ์ ปราสาททองโอสถ, วิเชียร ศรีมุนินทร์นิมิต

วัตถุประสงค์: *การรักษามาตรฐานในผู้ป่วยโรคมะเร็งระยะลุกลามเฉพาะที่คือการรักษานำหน้าด้วยยาเคมีบำบัดตามด้วยการผ่าตัด ยาสูตรมาตรฐานที่ใช้คือยาที่ประกอบด้วย anthracycline แต่ยาดังกล่าวมีผลอันไม่พึงประสงค์ได้แก่ ผมร่วง ผลข้างเคียงต่อหัวใจ ยา gemcitabine เป็นยาชนิดหนึ่งที่ได้ผลในผู้ป่วยโรคมะเร็งระยะแพร่กระจายและมีผลข้างเคียงน้อยกว่า จึงทำการศึกษานี้เพื่อศึกษาประสิทธิภาพของยา gemcitabine ร่วมกับ carboplatin ในผู้ป่วยดังกล่าว*

วัสดุและวิธีการ: *ผู้ป่วยโรคมะเร็งเต้านมในระยะ T3 หรือ T4 หรือมีการลุกลามไปที่ต่อมน้ำเหลืองที่รักแร้แบบ N2 จะได้รับการรักษาด้วยยา gemcitabine ขนาด 1,000 mg/m^2 ในวันที่ 1 และ 8 ร่วมกับ carboplatin ขนาด AUC x 5 ในวันที่ 1 ทุก 3 สัปดาห์ จำนวน 3 ชุด ผู้ป่วยที่มีการตอบสนองทางคลินิกจะได้รับการผ่าตัด และได้รับการรักษาเสริมด้วยยาสูตรเดียวกันอีก 3 ชุด ผลลัพธ์ปฐมภูมิ คือ อัตราการตอบสนองทางคลินิก ผลลัพธ์รอง ได้แก่ อัตราการตอบสนองทางพยาธิวิทยา ระยะเวลาปลอดโรค ระยะเวลารอดชีวิต และผลข้างเคียง*

ผลการศึกษา: *ผู้ป่วยเข้าร่วมการศึกษา 40 คน ระหว่างปี พ.ศ. 2547 ถึง พ.ศ. 2550 ระยะเวลากลางในการติดตามผล คือ 59 เดือน ประเมินประสิทธิภาพของยาจากผู้ป่วย 35 ราย และผลข้างเคียงของยาจากผู้ป่วย 40 ราย พบว่า 23 จาก 35 ราย (ร้อยละ 65) มีการตอบสนองทางคลินิก (partial response) ในผู้ป่วยที่ตอบสนองข้างต้น ได้รับการรักษาด้วยการผ่าตัด 22 ราย พบว่ามีการตอบสนองทางพยาธิวิทยาร้อยละ 51.5 (complete response ในผู้ป่วย 1 ราย และ partial response 17 ราย) ผู้ป่วยกลุ่ม triple-negative 7 รายมีการตอบสนองต่อยาเคมีบำบัดทั้งหมด อัตราส่วนผู้ป่วยที่มีชีวิตรอดและปลอดโรคที่ระยะเวลา 5 ปี คือ ร้อยละ 67 และ 62 ตามลำดับ ผลข้างเคียงที่พบได้มากที่สุด คือ การกดไขกระดูก ซึ่งอาการไม่รุนแรง*

สรุป: *ยา gemcitabine ร่วมกับ carboplatin เป็นสูตรยาที่ใช้ได้ง่าย ผลข้างเคียงไม่มาก สำหรับการรักษานำหน้าในผู้ป่วยโรคมะเร็งเต้านมระยะลุกลามเฉพาะที่ โดยเฉพาะอย่างยิ่งในกลุ่ม triple-negative อย่างไรก็ตาม ยังต้องมีการศึกษาต่อไปที่มีจำนวนผู้ป่วยมากขึ้นโดยเฉพาะในกลุ่ม triple-negative*