

The cost-effectiveness of neoadjuvant chemotherapy in women with locally advanced breast cancer: Adriamycin and cyclophosphamide in comparison with paclitaxel and gemcitabine

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Background: A decision analysis model was developed to assess the cost-effectiveness of adriamycin and cyclophosphamide (AC) in comparison with paclitaxel and gemcitabine (PG) in women with advanced breast cancer in Iran. **Materials and Methods:** This is a cost-effectiveness analysis performed as a cross-sectional study in Namazi Hospital in Shiraz, Iran. Patients were divided into two groups by random numbers, 32 women in the AC group and 32 women in the PG group. The costs were measured using the societal perspective and effectiveness of 2 regimens were assessed using tumor response. By a decision tree, the incremental cost-effectiveness ratio was calculated. In addition, the robustness of results was examined by sensitivity analysis. **Results:** The estimated total cost of AC and PG per patient was 1565.23 ± 765.31 and 2099.08 ± 926.99 , respectively. Response to treatment in AC and PG arm were 84% versus 75% respectively. The incremental cost-effectiveness ratio results showed AC is a dominate alternative. **Conclusion:** Overall, AC was a simple dominate strategy. In other words, AC was estimated to have a lower cost and greater effectiveness than PG.

Key words: Breast neoplasms, cost-benefit analysis, cyclophosphamide, doxorubicin, paclitaxel

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INTRODUCTION

Cancer is a global public health and economic concern.^[1] The number of new cancer cases is expected to increase from 10 million in 2010–2015 million in 2020. About 60% of those cases believed to occur in the less developed countries.^[2-5] Globally, the number of deaths from cancer in 2020 will reach about 11.8 million people.^[2] In Iran, cancer is the third main cause of death following cardiovascular diseases and accidents.^[3,4] The cost of cancer treatment has a high economic burden on the national health system budget. For example, in 2000, in England, 10% of the total spending on healthcare was for cancer treatment.^[5,6] The economic burden of cancer

in the Europe Union countries in 2009, was estimated at over 133 billion Euros.^[7] Among women, breast cancer is the main cause of disease and death. Each year billions of dollars are spent on treating breast cancer.^[8-10] In Iran, breast cancer is most frequently identified among other cancer that are diagnosed in women.^[11] Cancer chemotherapy is vital for patients with cancer. However, the available cancer treatments are usually very expensive. This situation not only threatens the lives and well-being of cancer patients but also jeopardize their financial security.^[12] Most women with locally advanced breast cancer cannot be treated surgically. Hence, neoadjuvant chemotherapy can be used for women with locally advanced breast cancer.^[13] The tendency to use neoadjuvant chemotherapy has increased due to its

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ability to reduce the size of the primary tumor. Neoadjuvant chemotherapy can be used as initiation, or induction or preoperative chemotherapy. The probability of treating advanced breast cancer increases if the women with it is initially treated by neoadjuvant chemotherapy.^[14,15] there are different chemotherapy regimens that can be applied to treat patients with advanced breast cancer. Selecting the chemotherapeutic regimens to depend on the clinical effectiveness of the drug in treating the patient and its cost.^[16] The most commonly used method to treat breast cancer includes anthracycline and taxanes. However, Adriamycin and cyclophosphamide (AC) regimen has been suggested as the standard regimen for patients with advanced breast cancer.^[14,17,18] Taxans is currently used in treating breast cancer. A study revealed that paclitaxel and gemcitabine (PG) regimen was found to have a promising effect on patients with advanced, metastasized and nonoperable breast cancer.^[19] These two regimens vary in efficiency, mechanism of action, toxicity, and side effects and synergistic effects.^[19] Furthermore, due to different expenditures of these two regimens, various economic impacts on the health system, and limited knowledge about the costs and their effectiveness, the aim in this study was to determine the optimal chemotherapy regimen for patients with locally advanced breast cancer by comparing the cost effectiveness of AC versus PG from the community perspective in Shiraz, Iran.

MATERIALS AND METHODS

Patients and treatments

A cross-sectional study was designed and a cost-effectiveness analysis was conducted in a period of 1 year (2013) on the total 64 breast cancer patients admitted to Namazi hospital, Shiraz, Iran. This center is a referral center in the south of Iran. Inclusion criteria were women with ages <65 years along with pathologically confirmed and progressive breast cancer, the Karnofsky Performance Score Index were ≥ 70 and renal, hepatic, and heart normal function. Exclusion criteria were all women up to 75 years with hypersensitivity reactions to the chemotherapeutic drugs; distant metastasis and node-negative cases. In this study, we include patients were in Stages IIB or III. In other words, all patients had locally advanced breast cancer.

According to these criteria, in this period, about 32 women received chemotherapy regimen including: adriamycin 60 mg/m², cyclophosphamide 600 mg/m² every 3 weeks for four cycles, and 32 women received chemotherapy regimen including: gemcitabine 1000 mg/m², paclitaxel 175 mg/m² every 3 weeks for four cycles. All the drugs were injected on the 1st day and gemcitabine was injected on days 1 and 8. Therefore, sampling was not done and all patients were included in the study.

Evaluation and outcome measurement

Effectiveness and costs were used in the current cost-effectiveness evaluation. To measure the effectiveness, we used tumor size. Tumor size has been an important prognostic factor of distant metastasis in several studies.^[20,21] To measure the effectiveness of each group, before treatment, the history and clinical examination was performed and tumor size by clinical examination with special caliber was measured and recorded in the form of data collection, then treatment was started. Finally, after completing four courses of treatment, the final evaluation was conducted and tumor size for evaluating the clinical response was controlled. Tumor response was measured according to the RECIST criterion. Complete response was no evidence of tumor; partial response was more than 30% decrease in tumor dimension. Less than 30% decrease or less than 20% increase in tumor dimension was considered no change in tumor size. Tumor progression was more than 20% increase in tumor dimension. Finally, total of complete response and partial response was defined as the response to treatment, total of tumor progression and no change in tumor size was defined as the nonresponse to treatment. The patient costs were recognized and calculated from the societal viewpoint. These items were medical direct costs (chemotherapy, visits, laboratory, radiology) and nonmedical direct costs (traveling, accommodation, phone, auxiliary equipment) and indirect costs (time spent by the patient, time spent by the patient's accompany). Indirect costs are determined using the human capital approach. In our 1 year study period, the discount rate was not used. After the last cycle of chemotherapy, oral interview with patients was performed and then, the cost data were collected.

Perspective

The community perspective was adopted for this study. It is the most appropriate choice because it represents the viewpoint of the society as a whole rather than that of any special group.^[22]

Analysis

SPSS is a widely used program for statistical analysis in social science in this study, we used SPSS for descriptive analysis and TreeAge 2011. TreeAge software is used for build models to study simple and complex problems to choose the best alternatives. This software uses sophisticated analysis and reporting tools to your model, including decision analysis, cost-effectiveness analysis, sensitivity analysis, and Monte Carlo simulation. The expected costs and effectiveness were accounted using a decision tree. Sensitivity analysis was performed for improving the accuracy of the study. Decision tree algorithm is shown in Figure 1.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences.

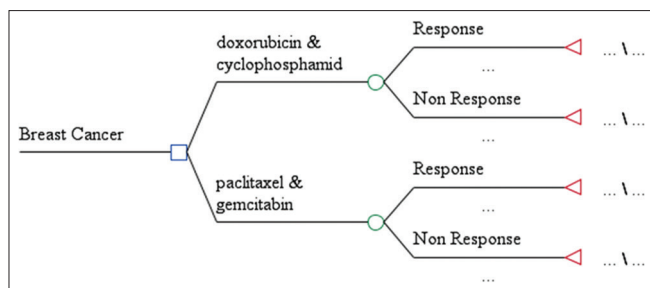


Figure 1: Decision tree algorithm for neoadjuvant chemotherapy in women with locally advanced breast cancer

RESULTS

Of 64 female patients, 74% were up to 40 years old age, 62.5% were married, 91% were educated, and 95% were insured. Demographic data are shown in Table 1.

The mean cost of chemotherapy in the AC and PG arms was 1157.39 and 1646.39 US\$, respectively. Hence, cost of chemotherapy drugs was the highest medical direct costs [Table 2]. The highest nonmedical direct costs in AC and PG were traveling costs (25.88 US\$) and auxiliary equipment costs (29.48 US\$), respectively. The accompany costs were the highest type of indirect costs in both arms (33.43 and 44.66 US\$ in AC and PG, respectively).

According to Table 3, the percentage of the response to treatment in AC arm was more than PG arm. Among 32 patients who received AC chemotherapy regimen, 27 patients showed a response to treatment. In this arm, complete response was seen in 10 patients and partial response was seen in 17 patients. No tumor progression was seen in AC arm, but 5 patients had no change in tumor size. In patients who received PG chemotherapy regimen, 24 patients showed response to treatment. No complete response was seen in GP arm, but the partial response was seen in 24 patients. Tumor progression and no change in tumor size were seen in 2 and 6 patients, respectively.

As a shown in Figure 2, the expected cost in AC and PG arms were 39170.53 US\$ and 43336.69 US\$, respectively. Furthermore, the expected effectiveness in AC and PG arms were 0.74 and 0.62, respectively. Furthermore, incremental cost-effectiveness ratio (ICER) was -37307.089 dollars. AC was estimated to have a lower cost and greater effectiveness than PG. These results showed that the AC was dominate versus PG. The rejected strategy, PG chemotherapy regimen, is displayed with hash marks.

In comparison between two chemotherapy regimens, AC and PG were dominate and dominated, respectively. AC is more effective and low cost but PG is less effective and more costly [Figure 3]. The favored strategy, AC chemotherapy regimens, is shown with the triangle, while the rejected

Table 1: Demographic characteristics of breast cancer patients

Variable	n (%)
Age	
<40	17 (26)
>40	47 (74)
Marital status	
Married	40 (62.5)
Single	24 (37.5)
Education	
Educated	58 (91)
Illiterate	6 (9)
Insurance	
Insured	61 (95)
Uninsured	3 (4)

Table 2: The costs used in analysis (US\$)

Type of costs	Type of chemotherapy regimen	
	AC	PG
Medical direct costs		
Chemotherapy	1157.39±494.59	1646.39±638.69
Visits	28.53±17.18	28.89±16.29
Laboratory	81.18±49.65	96.17±60.58
Radiology	162.05±89.27	172.84±84.15
Nonmedical direct costs		
Transportation	25.88±23.40	23.90±21.61
Accommodation	11.48±10.90	15.31±12.42
Phone	9.84±4.57	10.05±7.48
Medical equipment	25.86±22.14	29.48±28.19
Indirect costs		
Time costs imposed on the patient	29.59±22.51	31.39±22.83
Time costs imposed on the patient's attendant	33.43±31.10	44.66±34.75
Total	1565.23±765.31	2099.08±926.99

AC=Adriamycin and cyclophosphamide; PG=Paclitaxel and gemcitabine

Table 3: The effectiveness of adriamycin and cyclophosphamide and paclitaxel and gemcitabine regimen in breast cancer

Effectiveness	Type of chemotherapy regimen			
	AC		PG	
	Response	Nonresponse	Response	Nonresponse
Number of patient (%)	27 (84.4)	5 (15.6)	24 (75)	8 (25)

AC=Adriamycin and cyclophosphamide; PG=Paclitaxel and gemcitabine

strategy, PG chemotherapy regimens, is shown with a square.

Sensitivity analysis

Probabilistic and one-way sensitivity analysis were done. In one-way sensitivity analysis in Figure 4, we increased all parameters to 20%. Then, we investigated how changes in model parameters would affect the ICER using one-way sensitivity. Tornado diagram showed that ICER has the

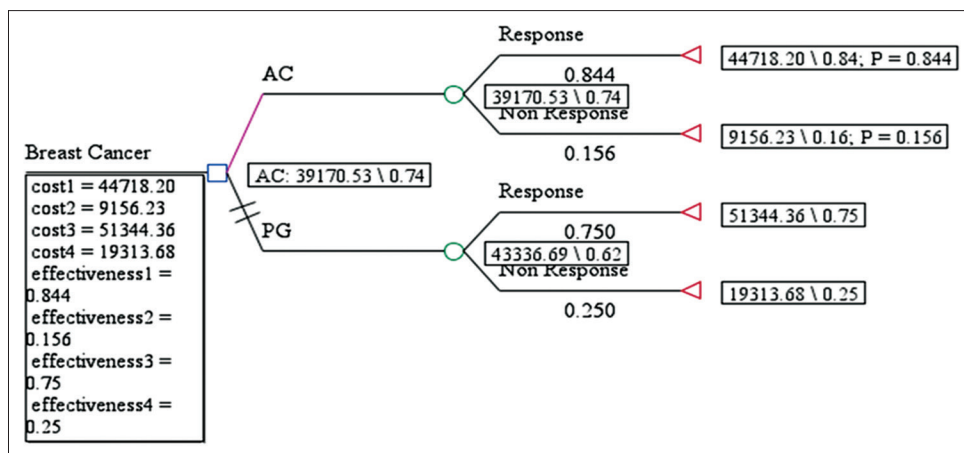


Figure 2: Results of decision tree algorithm

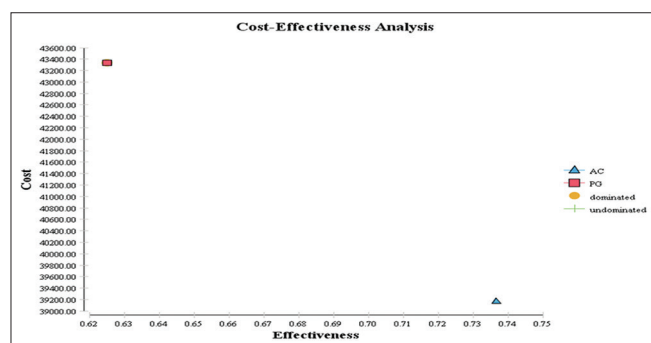


Figure 3: Cost-effectiveness analysis of adriamycin and cyclophosphamide versus paclitaxel and gemcitabine

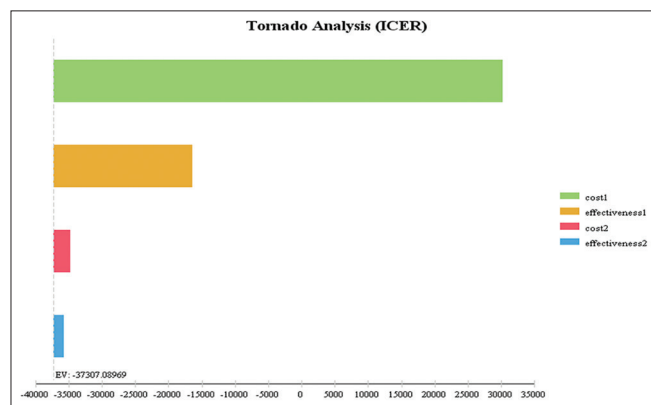


Figure 4: Results of one-way sensitivity analysis (tornado diagram)

highest sensitivity to changing in the cost of cases who response to AC and the lowest sensitivity to changing in effectiveness of cases who nonresponse to AC.

The incremental cost-effectiveness plane shows Monte Carlo simulation of incremental costs and effectiveness of using AC for treatment of breast cancer versus PG. For each one of the 10,000 iterations, values for parameters were randomly selected from their distributions, and an ICER was calculated. These results showed that the AC was dominate versus PG in 97% of the simulations [Figure 5].

DISCUSSION

Economic evaluation studies have become an essential factor in the assessment of new interventions or treatments, such as neoadjuvant chemotherapy.^[23,24] The goal of the current study was the evaluation of the cost-effectiveness chemotherapy regimens including AC in comparison to gemcitabine and paclitaxel in patients with advanced breast cancer. According to the findings of this study, the average cost of chemotherapy regimens PG with 2099.08 US\$ was more than that of AC chemotherapy regimens with 1565.23 US\$, and the difference was statistically significant ($P = 0.001$). The main reasons for high costs of PG were the cost of chemotherapy drugs. In our study, out of total costs, chemotherapy costs were 73% in the AC and 78% in PG arm. Bernard *et al.* showed that 70% of the total costs in AC was associated with the cost of chemotherapy.^[25] Furthermore, in the Chen *et al.*, study 65% of total costs in PG was related to the cost of chemotherapy.^[26] Chen *et al.* in their study in 2001 concluded that the costs of chemotherapy regimens containing paclitaxel and gemcitabine were more than those of chemotherapy regimens containing paclitaxel and carboplatin. They stated that the high cost of the PG treatment was as a result of the costs of chemotherapy drugs and the gemcitabine on the 8th day.^[26] In previous studies, the low cost of AC regimen was due to costs of chemotherapy drugs.^[25,27,28] The results of this study showed that the response to treatment in AC chemotherapy regimen with 84% was higher than PG chemotherapy regimen with 75%. In a study which conducted by Colomer *et al.* On 35 breast cancer patients, 2 weeks chemotherapy regimen which contains gemcitabine and paclitaxel for patients with advanced breast cancer was examined. A total of 43 patients with advanced breast cancer in every 2 weeks received paclitaxel 150 mg/m² and gemcitabine 2500 mg/m² for 8 periods in the first and 8 days. Overall, response rate in this study was 71% which 11 patients were fully responded to the treatment (26%).^[19]

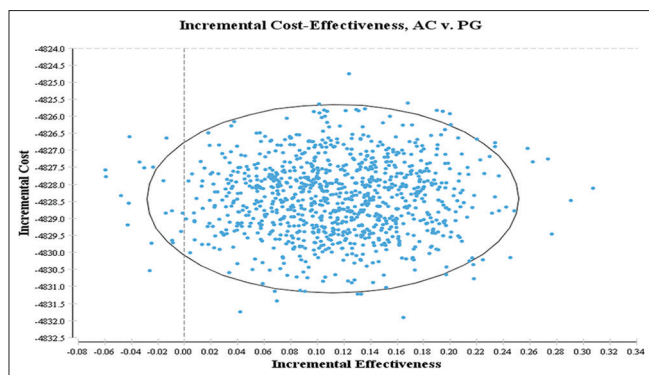


Figure 5: Incremental cost-effectiveness plane

When compared to PG, AC is cost-effective and dominate because the expected cost was 39170.53 US\$ and the expected effectiveness was 0.74. Therefore, AC is dominate as compared to PG (fewer cost and more effective). It can be due to the higher cost of chemotherapy treatments in the PG and perhaps the gemcitabine in the 8th day. Even though we could not find any similar study that compares the AC and PG treatment regimes, but Bernard *et al.* in the study which aimed to evaluate the AC with docetaxel and cyclophosphamide (TC) using adjuvant method concluded that AC therapy is more cost-effective. Bernard finds that TC has higher cost utility than AC, 8251\$ per QALY.^[25] Younes and *et al.* showed that cost-utility of TC therapy relative to AC is 16753\$ higher for each QALY. Higher cost-utility of TC could be due to that replacing AC with TC impose more cost to patients and is more expensive. However, the fact that cost-effectiveness of AC is higher than PG could be due to that AC treatment regime impose fewer cost and is cheaper.^[27] Overall, the results showed that AC versus PG was dominated in the treatment of patients with advanced breast cancer. Also, ICER was -37307.089 dollars that means AC saves 37307.089 dollars per each additional response to treatment. Therefore, it is recommended that oncologists should use AC instead of PG in the treatment of these patients. Tornado chart showed that ICER has the highest sensitivity to changing in COST of patients who respond to AC and the lowest sensitivity to changing in effectiveness of patients who nonrespond to AC.

CONCLUSIONS

Based on the results of the study, AC is cost-effective, as compared to PG, and it is dominated because the expected cost was 39170.53 dollars and the expected effectiveness was 0.74 in the AC arm whereas the expected cost was 43336.69 dollars and the expected effectiveness was 0.62 in the PG arm. Also, ICER was -37307.089 dollars (using AC saves 37307.089 dollars per each additional effectiveness). Therefore, it is recommended that oncologists should use AC instead of PG in the treatment of these patients.

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Conflicts of interest

There are no conflicts of interest.

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