Effectiveness of a Novel Option of BC Patients with Stage III ($T_{any}N_3M_0$)

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RESEARCH

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ABSTRACT

Background: Breast cancer (BC) stage III treatment options are very widely and may consist of mastectomy and radiation for local treatment and hormone therapy or chemotherapy for systemic treatment. Among this stage category BC stage IIIC (T1-4N3M0) is considered advanced, that is why necessary to find effective treatment options for this stage patients. In this study results support us believed that BC stage III tumors are TUBB3-expressed tumor and the combination of gemcitabine and cisplatine has to be highly active regiment as first-line treatment BC stage III (T_1-$4N_3M_0$) patients. The treatments option that systemic chemotherapies and local therapy methods to follow each other can be reasonable scheme for BC stage IIIC (T1-4N3M0) patients.

Key Words: Breast cancer stage IIIC; Neo-adjuvant and adjuvant chemotherapy; Systemic and local treatment; Tumor biology; Gene expression.

INTRODUCTION

Breast Cancer (BC) stage III (a, b, c) treatment options are very widely and may consist of mastectomy and radiation for local treatment and hormone therapy or chemotherapy for systemic treatment [2, 3]. Among this stage category BC stage IIIC (T1-4N3M0) is considered as advanced and requiring more intently attention, because cancerous cells can spread to distant organs any moment. National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology protocols are recommended several effective treatment options for this rare and aggressive type of malignancy, but does not always lead to a favorable outcome. In the previous study we retrospectively analysis BC stage IIIC (T1-4N3M0) treatment outcome in 65 patients [1]. Only 33 patients out of 65 receiving neoadjuvant chemotherapy in this group benefited from treatment and afterward had radical mastectomy surgery. In this study, we used treatment option for BC stage IIIC (T1-4N3M0) patients, in which during treatment period

systemic chemotherapies and local therapy methods to follow each other.

PATIENTS, MATERIALS AND METHODS

This is a single-arm study including 35 primary patients with BC stage IIIC (T1-4N3M0). The study protocols were reviewed and approved by the Institutional Review Board. The written informed consent was obtained from all patients before to their inclusion in the study. Females aged 34-62 years with histological confirmed stage IIIC (T_1-$4N_3M_0$) were eligible in the study. Eligible patients were treated with the following: gemcitabine 1250 mg/m2, intravenous infusion over 30 minutes on day 1 and 8 plus cisplatin 75 mg/m2, intravenous infusion over 1 hour on day 1. Chemotherapy was repeated every 21 days and was administered for maximum of six cycles using scheme as described in figure 1. Treatment processes would be discontinued in case of unacceptable toxicity, treatment delay longer than 2 weeks, disease progression or patient refusal. Patients were evaluated regularly every three weeks with a physical examination, complete blood picture, laboratory studies and toxicity assessments were performed. Appropriate radiological assessments were performed for treatment response documentation. Patients with response status were continued treatment protocol to horizontal direction; patients with no response outcome were offered the vertical direction of the protocol (Figure 1). In term of response criteria, the size of measurable lesions was determined before each course of therapy and reported as the product of the longest diameter and its perpendicular. Tumor response was assessed radiology by computed tomography after every two courses of chemotherapy, according to the NCCN guideline. The primary endpoint was progression-free survival (PFS). The duration of an objective (complete or partial) response was measured from the time the response was first documented to the data of disease progression. Time to progression was defined as the period from the time of treatment to that of disease progression or discontinuation due to death or drug-related toxicities. The expression level of TUBB3, RRM1, TYMS, and ERCC1 genes were investigated in normal and cancerous tissues. The genes expression levels were calculated by the formulae $2-\Delta\Delta Ct$, using the relative Ct data. The analysis was conducted in the RT-PCR machine (CFX96, Real-Time system, BioRad, US).

RESULTS

Total of 35 women with breast cancer stage IIIC (T_1-$4N_3M_0$) was collected in the inspected group from June (2015) to November (2017). The same categories patients that refused participate in the research were considered as the control group. The median observation time was 28, 9 with a range from 12 to 53 months. The primary endpoint was progression free survival. The control group patients' outcome did not demonstrate in this study, but these results were used for comparative analysis with the inspected group in the discussion part of this paper.

The study group consisted of a woman with a median age of 62, ranging from 34 to 67. All patients have treated by scheme that demonstrated in figure 1 using chemotherapy with Gemcitabine 1250 mg/m2, intravenous infusion over 30 minutes on day 1 and 8 plus cisplatin 75 mg/m2, intravenous infusion over 1 hous on day 1. Human epidermal growth factor receptor 2-positive (Her2) breast cancer was in seven patients and only two of them received target therapy (Trastuzumab) because of economics condition. Five patients had triple-negative (TN) BC.

In the study were assessable only 31patients of 35 enrolled. Three women after 4 cycles neo-adjuvant polychemotherapy (NPCT) had complete responses (CR), refused surgery and did not follow up treatment (Table 1). Additional 2 cycles NPCT was reported only in one patient: after radiotherapy, she was ready to surgery treatment and oncology doctors counselled to miss 2 APCT and continue therapy with biological subtype corresponding drug. Then the patient was joined to the basic observation group. The median number of chemotherapy cycles for 30 patients was 6 cycles. These 30 patients had full horizontal scheme treatment shifting systemic and local therapy as demonstrated in figure 1. Thirty-one patients were assessable for observation after full treatment process. The tumor progression was observed in nine patients with the

median time progression 14 months (95% confidence interval 7 to 31 months). The tumor progression disease site in these patients were a bone (4/9), intra-thoracic lymph node (2/9), liver (1/9), lung (1/9) and brain (1/9) metastasis. Four patients from nine had Her2-positive receptor and three of them did not receive corresponding target treatment (Trastuzumab). In these patients had bone and brain progression and short PFS from 7 to 24 months, two patients, dead. In the 22 patients, disease did not progress until end of study observation (Table1).

Table 1. The treatmnet outcome of BC stage IIIC (T1-4N3M0) patients.

Patients characteristics	Number of patients (n)
Enrolled patients	**35**
Stable disease (SD) – non operabel	1
Patient who refuse surgery	3
Assessable patients	**31**
No progress	22
a) Complete response (CR)	15
b) partial response (PR)	16
Progress	9
a) bone metastasis	4
b) intra-thoracic lymph node	2
c) liver	1
d) lung	1
f) brain	1

RNA was extracted from formalin-fixed paraffin-embedded tumor materials in 31 patients. From 31 tumor materials 21 were observed high level of TUBB3 (β-tubulin) gene expression. Excision repair cross-complementing group 1 (ERCC1) gene was expressed in 15 patients. In 11 patients high expression were found in both genes (TUBB3+ERCC1). TUBB3 gene was high expression level in all nine patients with short tumor progression time.

DISCUSSION

The study designed basing on the previous retrospective statistical analysis report and corresponding research articles information [1, 12, 9]. As recommend NCCN protocols the frontline neo-adjuvant chemotherapy were taxanes (T) and anthracyclines (AT) in retrospective and perspective control groups patients with stage IIIC. Only 33 out of 65 and 57 out of 100 patients receiving neo-adjuvant chemotherapy were benefited and afterwards had radical mastectomy surgery in these groups [1]. As the taxanes (T) and anthracyclines (AT) were frontline neo-adjuvant chemotherapy in these groups, the TUBB3 gene expression was investigated due to suggested, that resistance of T- and AT- could be relate alteration of this gene expression [6, 4, 7, 8, 10]. The study of TUBB3 gene expression was demonstrated that gene overexpressed in 71% and 65% tumor materials in the retrospective and control group patients respectively [1]. High number of tumors withTUBB3 gene overexpression was found in the patients of inspected group also: 21 tumor materials out of 31 observed high level of TUBB3 expression. The results of these three studies suggest that BC stage III tumors can be considered as the TUBB3-expressed tumors. It known, that most of FDA-approved tubulin inhibitor drugs including taxanes and vinca alkaloids targeted β-tubulins [6, 4, 7, 8]. Among these β-tubulin isoforms, β III-tubulin is the most intensively studied due to evidence regarding its role in taxane resistance [12]. The majority of these studies concerning TUBB3 expression mainly focused on its potential predictive value for taxanes efficacy. We suggest of the possibility is less efficiency to outcome of tubulin inhibitor drugs because a lot of TUBB3-expression cells in

the BC stage IIIC patient's tumor material. The based on the current information of BC stage III tumor biology for inspected group patients were selected combination regime with gemcitabine (G) plus cisplatine (S), versus taxanes and anthracycline-based regimens. Authors reported the efficient results of treatment using G+S as first line chemotherapy in metastatic and triple negative BC [12, 9], but did not investigate tumor biology. This study reasonable treatment option was advantageous in 71% patients receiving G+S combination regimens (Figure 2). At least 3 studies reported the results of the use of G+S in breast cancer patient as first-line treatment [12, 9, 11], and our results were similar to and perhaps, in some cases better, due to the novel scheme of treatment. The optimal schedule of administration of combination chemotherapy was 4 cycles of NPCT before surgery and 2 cycles of APCT a 2-3 weeks later surgery. The treatment option included an additional 2 cycles of chemotherapy after surgery versus standard protocol, that used 8 and more cycles chemotherapy before the local therapy (NCCN guideline). The aim of adjuvant treatment after surgery or radiotherapy is to lower the risk of cancer coming back in the future. In this case, we use recommendation [5] that suggested killing off any cancer cells that have broken away from the main tumors before a local operation. All enrolled patients had a good response after 4 cycles NPCT therapy and continue therapy scheme (in our case surgery), and an additional 2 APCT. It is interesting to mention that there is a higher response rate (RR) and longer time to progression (TTP) by comparisons with the control group.

The overall objective response rate was 97.1 % in the 31 enrolled patient: 15 patients had complete response (CR) and 16 patients partial (PR). In addition, tumor growth control (overall response (97.1%) + stable disease (2.9%)) was 100%, so a greater proportion of patients derived considerable benefit from this therapy option. The tumor progression time (TTP) was 7 months after ended full treatment processes and progression-free survival (PFS) was from 7 to 31 months, the median time to progression was 14 months in nine BC stage III (T_1-$4N_3M_0$) patients. The majority of BC stage III or metastatic breast cancer trials published so far are underpowered to detected small survival gains, particularly, for second and subsequent lines of chemotherapy. The major advantage for this treatment option is a short therapy time because it is important to balance the side effects profile.

CONCLUSION

Thus, our results support us believed that BC stage III tumors are TUBB3-expressed tumor and the combination of gemcitabine plus cisplatine has to be highly active regiment as first-line treatment BC stage III (T1-4N3M0) patients. The treatments option that systemic chemotherapies and local therapy methods to follow each other can be reasonable scheme for BC stage IIIC (T1-4N3M0) patients, but large-scope studies are needed to conform our results

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PEER REVIEW

Not commissioned. Externally peer reviewed.

FIGURES

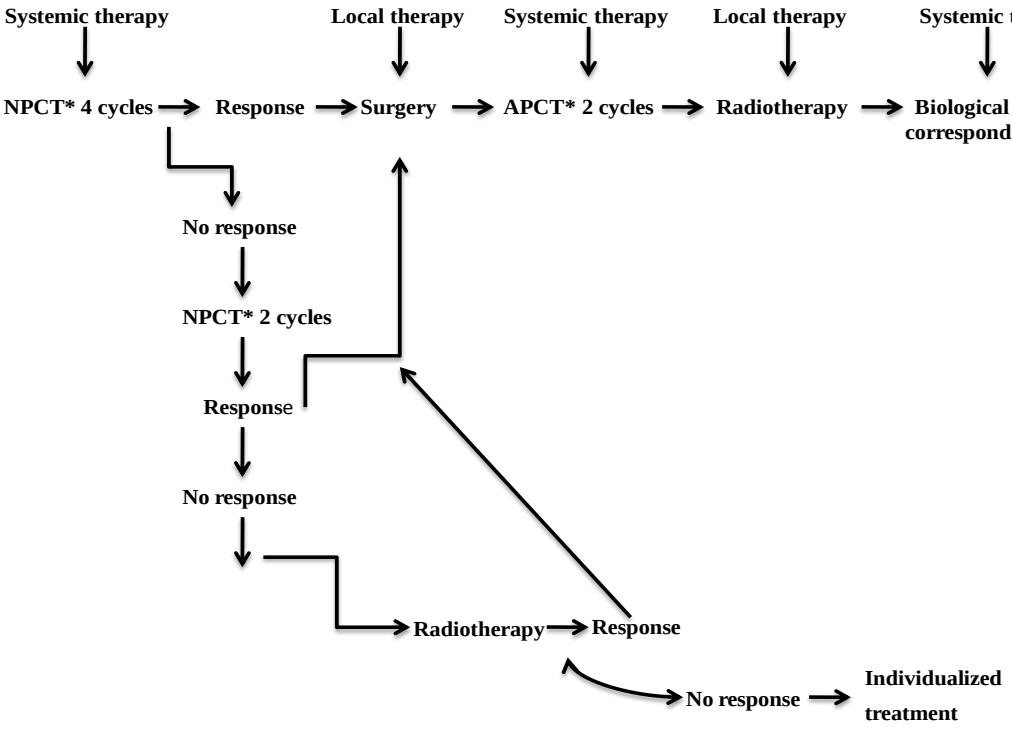

Figure 1. The scheme demonstrate to sequence of systemic and local therapies in patients with breast cancer stage IIIC ($T_{1-4}N_3M_0$)

NPCT*-neo-adjuvant chemotherapy; APCT*-adjuvant chemotherapy

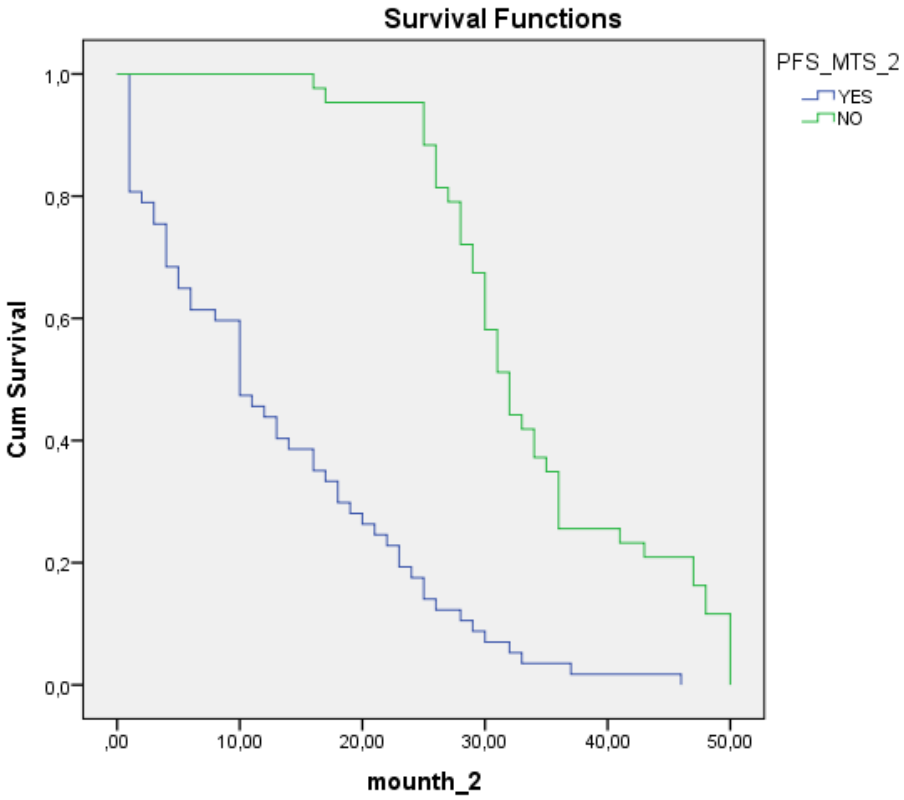

Figure 2