Study the Glucose Transport, Angiogenesis and Apoptosis Behavioral through Chemotherapy Treatment According to Receptors Status in Women with Breast Cancer

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Abstract

Background: Glucose transporting into cells, angiogenesis, and apoptosis are the main factors that inducing the progression of many types of cancers including breast cancer. BC progression was seen as a multi-step process involving progressive changes from normal to hyperplasia with and without atypia, carcinoma in situ, invasive carcinoma, and metastasis.

Aim: Assessment the role of glucose transport-1 (GLUT-1), vascular endothelial growth factor (VEGF), and cluster of differentiation factor(CD44) as a glucose transporting into cells, angiogenesis, and apoptotic factors in women with BC whom receiving chemotherapy.

Method and Subjects: 120 women with BC included in this study as a patients group as well as 120 apparently healthy women as control. The women with BC is divided into sub-groups depending on chemotherapy treatment status. GLUT-1, VEGF, and CD44 were investigated by ELISA method.

Results: This study suggested that highly significant differences in the mean and standard division of GLUT-1 and VEGF in all cases of women with BC compare to control group (P-Value< 0.05). The levels of GLUT-1 was highly significant difference between two subgroup have Her-2 positive and negative ($p < 0.001$), and the levels of VEGF, and CD44 in patients subgroups were significant ($p< 0.05$).

Conclusion: The following up of the progression and responding to chemotherapy treatment may be more easy by estimation the glucose transporting, angiogenesis, and apoptotic markers in women with BC.

Keywords: *Breast cancer, glucose transport, angiogenesis, apoptosis.*

Introduction

The plasma membranes of most mammalian cells, except those of the proximal kidney and small intestine, have a passively mediated transport system for glucose. Facilitative entry of glucose into the cell is controlled by GLUTs, structurally related proteins that are encoded by a gene family and are expressed in a tissue-specific manner[1,2]. Most cells contain at least one glucose transporter isoform, and many contain more than one. In most cell types, GLUTs mediate a net uptake of glucose[3]. GLUT1 is the most ubiquitously distributed of the transporter isoforms. It is found in virtually all tissues of the fetus and in many tissues and cell types of the adult[4]. GLUT1 has a very high affinity for glucose[5]. VEGF actions are mediated through binding to two receptor tyrosine kinases, VEGFR-1 and VEGFR-2. Activation of these receptors by VEGF triggers the phosphorylation of a multitude of proteins that are active in signal transduction cascades[6]. VEGF expression is increased in the majority of cancers examined to date. The list is

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extensive and includes hematological malignancies[7]; colorectal cancers[8]; hepatocellular carcinoma[9]; lung, thyroid, breast, gastrointestinal tract, kidney, and bladder cancers; ovary and uterine cervix carcinomas[10]. CD44 is a family of non-kinase, single span trans-membrane glycoproteins expressed on embryonic stem cells and in various levels on other cell types including connective tissues and bone marrow[11,12]. CD44 expression is also up-regulated in subpopulations of cancer cells and is recognized as a molecular marker for cancer stem cells (CSC)[13]. In Iraq, breast cancer ranks the first among the top ten malignant neoplasms affecting the community; comprising 19.5% of total (4996 cases) and 34.3% of female cancers (4922 cases)[14]. During 2016, 897 women died from that disease which is the registered as the first cause of cancer related mortality among Iraqi females (23.6%) and the second overall among males and females (12.1%) after bronchogenic cancer[15]. The aim of this study to investigate the role of glucose transport-1 (GLUT-1), vascular endothelial growth factor (VEGF), and cluster of differentiation factor (CD44) as a glucose transporting into cells, angiogenesis, and apoptotic factors in Iraqi women with BC whom receiving chemotherapy.

Materials and Method

Specimens collection: This study was performed during the period from Dec 2018 to May 2019 in biochemistry laboratory, collage of medicine, Babylon university. One hundred and twenty patients were previous diagnosis with BC and receiving chemotherapy in oncology center in Merjan Teaching hospital.

Estimation of GLUT-1, VEGF, and CD44 by ELISA: GLUT-1, VEGF, and CD44 levels were estimated by sandwich ELISA depending on the instructions of the manufacture provided with kits (Sunlong/China).

Statistical analysis: Statistical analysis for assessment of GLUT-1, VEGF, and CD44 in different groups was performed by ANOVA test with using SPSS software. Significant differences were established at $p < 0.05$.

Results

The receptors status of women with BC included in this study is shows in table-1:

Table 1: Estrogen, progesterone, and Her-2 status of patients group

Receptors status	Number (%) N=120
ER status	
P	55(46)
N	65(54)
PR status	
P	66(55)
N	54(45)
Her-2 status	
P	36(30)
N	84(70)

The levels of GLUT-1, VEGF, and CD44 in all patients and control groups are illustrate in table-2:

Table 2: Levels of GLUT-1, VEGF, and CD44 in all patients and control groups

No	Parameters	Women with BC mean± SD (N=120)	Women without BC mean± SD (N=120)	P-Value
1	GLUT-1 (ng/ml)	121±9.3	67±5.1	0.0001
2	VEGF (ng/ml)	23.2± 3.8	11.3± 2.7	0.0001
3	CD44 (ng/ml)	217± 5.9	239.5± 4.1	0.0004

The levels of GLUT-1 was highly significant difference between two subgroup have Her-2 positive and negative ($p< 0.001$), and the levels of VEGF, and CD44 in patients subgroups were significant ($p< 0.05$). This results of patients whom receiving chemotherapy depending on receptors status are illustrate in figure-1 and table-3:

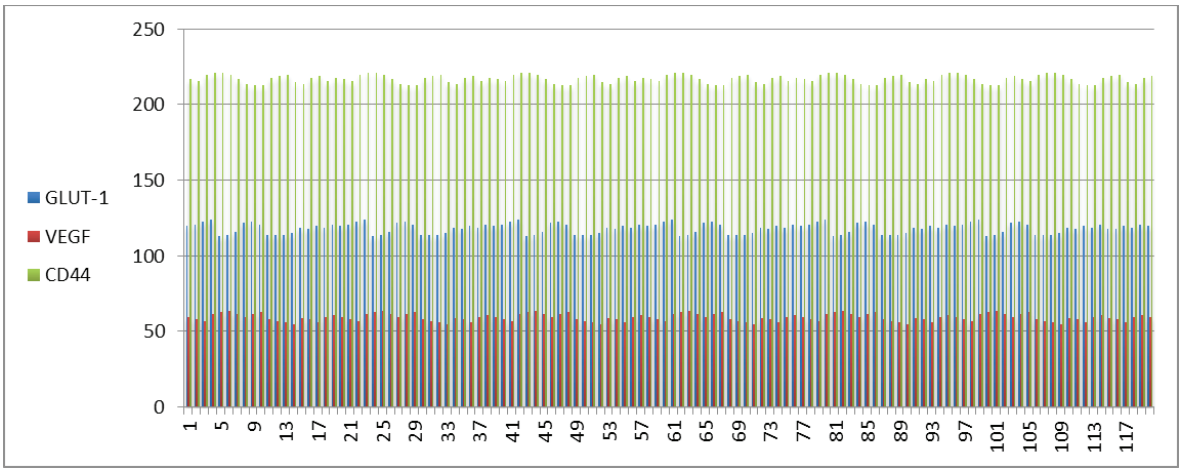

Fig. 1: Expression levels of GLUT-1, VEGF, and CD44 (ng/ml) in patients group

Table 3: Levels of GLUT-1, VEGF, and CD44 in patients group depending on receptors status

No	Receptor status	GLUT-1 Mean± SD	VEGF Mean± SD	CD44 Mean± SD
1	ER P N	 119± 2.7 * 114± 1.9	 57± 1.9 56± 1.5	 215± 7.7 211± 8.8
2	PR P N	 117± 2.6 * 112± 1.6	 55± 1.3 53± 1.2	 217± 9.2 214± 6.9
3	Her-2 P N	 119± 2.5 ** 111± 1.3	 57± 1.5* 51± 1.4	 217± 5.6* 210± 7.4

*significant
**highly significant

Discussion

Worldwide, BC is the most common cancer in women. The new cases of women with breast cancer in 2018 were more than 250 000 in the UAS, and breast cancer will be diagnosed in 12% of all women in the USA over their lifetimes[16]. Globally, about 2.1 million women were estimated with breast cancer in 2018[17]. Breast cancer is a heterogeneous disease witch results from a series of genetic and epigenetic events that lead to dys-regulation of cell growth, circumvention of apoptosis, and development of the ability to invade the underlining tissue through the basement membrane[18]. In the present study, we investigated the levels of GLUT-1, VEGF, and CD44 as glucose transporter system, angiogenesis, and apoptotic marker, respectively. The results showing highly significant differences in the mean and standard division of GLUT-1 and VEGF in all cases of women with BC compare to control group. GLUT-1 is multi-pass protein located in the cell membrane and it essential for interring the glucose molecules into cells to complete metabolism such as glycolysis to provide energy for cancers cells[19]. GLUT1 is responsible for the low level of basal glucose uptake required to sustain respiration in all cells. Expression levels of GLUT1 in cell membranes are increased by reduced glucose levels and decreased by increased glucose levels. The levels of this protein was found to be more expressed in women with BC compare to control and this increase the supporting hypothesis that say of "the cancers cells fed on sugar". Through the angiogenesis process, the cancer cells building a new blood vessels and increase the expression of VEGF[20]. The results suggested that highly expression of VEGF in patients group and this increase the probability of building a these vessels and promoting the neovascularization and in results increase the proliferation of tumors and cancer progression. The association between a gradual increase in CD44 isoform expression and tumor progression

from less malignant stages to more advanced stages is another indirect indication of CD44 involvement in the malignant process. This concept isperhaps best illustrated by a report describing CD44 expression in colorectalcancer patients[21].This study suggested that the expression of GLUT-1 and VEGF in positive status of ER and PR was highly significant in subgroups of patients withBC whom receiving chemotherapy and the expression of VEGF and CD44 not appear in these subgroups. This indicatethat the cells having ER, PR were more suitability to incidence of breast cancer more than negative status. Other finding was obtaining from the results suggested that increasing the proliferation and tumor progression were more in women with Her-2 positive status because it highly expressed of GLUT-1, VEGF, and low expression of apoptotic marker, CD44. In conclusion, the following up of the progression and responding tothe chemotherapy treatment may be more easy by estimation the above markers in women with BC.

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