JKBMS, Vol.1, No.1, P.64-73, 2015 https://doi.org/10.56056/amj.2015.08

Immunoexpression of Bcl-2 in Breast Carcinoma: Association with Clinicopathological Parameters

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Abstract

Background and Objectives: Breast cancer is the most common malignancy in women. It is an immensely heterogeneous disease, characterized by a broad variety of clinical development. The research in recent years has focused on finding new markers of prognostic significance. Bcl-2, the protein product of the Bcl-2 gene, is a member of the Bcl-2 family of proteins that play a crucial role in a complex mechanism of apoptosis. It was recently proposed that Bcl-2 could inhibit cancer progression. Aims of the study: To evaluate the role of Bcl-2 oncoprotein expression in patients with breast carcinoma and its relation with various clinic pathological parameters.

Patients and Methods: Hundred cases of primary breast cancer were included in this prospective retrospective study. The cases were collected from Rizgary Teaching Hospital and Private Laboratories during a period of ten months from February to November 2013. The expression of Bcl-2 oncoprotein was evaluated immunohis to chemically; the findings were correlated with the age of the patients, size, type and grade of the tumor, lymph node status, vascular invasion, and the estrogen and progesterone receptors.

Results: Bcl-2 oncoprotein was detected in 61 cases of primary breast cancer (61%). In this study the majority of estrogen and progesterone receptors positive cases, (71%) and (59%) respectively, showed positive Bcl-2 oncoprotein expression, (P=0.030) and (P=0.001) respectively. No significant correlation with the age of the patient, size, type, grade of the tumor, lymph node status nor with lymphovascular invasion could be found, (P=0.218), (P=0.410), (p=0.947), (p=0.938), (p=0.190), (P=0.370) respectively.

Conclusions: Bcl-2 oncoprotein was frequently expressed in primary breast cancer. This study revealed a significant correlation between Bcl-2 and the estrogen and progesterone receptors. Our results suggest that Bcl-2 expression may be related to hormonal regulation. Larger patient study groups with a long follow up period will be helpful to clarify the prognostic significance of Bcl-2.

Introduction

Breast cancer is the most common type of non-skin cancer in women all over the world and the second leading cause of cancer death among women after lung cancer.[1] Breast cancer continues to be an important health and management problem worldwide, more than one million cases of breast cancer are diagnosed worldwide every year.[2] One of the greatest challenges in breast cancer management is to accurately predict outcome and the lymph node-negative subset of patients there is variability in prognosis, and we have no reliable means of determining which patients will survive without adjuvant systemic therapy.[5] There is therefore great for each patient so that we can determine who will benefit from adjuvant therapy.[3] A number of factors are used to assess the risk of developing metastatic disease and death, including lymph node involvement, tumor size, nuclear and histologic grade, age, hormone receptor expression and Her2/neu status.[(4)] Lymph node involvement is the most reliable predictor of metastatic relapse, yet within the lymph node-positive subset need to identify new prognostic markers that will assist in patient selection for adjuvant therapies. More- over, these markers can assist in selection of bio specific therapies once drugs that target these markers become

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available.[4,6] Bcl-2 is an intracellular membrane associated protein of 24-kilodalton. It has been localized in the nuclear envelope, endoplasmic reticulum, and outer mitochondrial membranes of hematopoietic and lymphoid cells, neurons, many epithelial cells, and endocrine influenced glandular epithelium such as the thyroid, prostate, endometrium, and breast.[7] Bcl-2 was first identified as an antiapoptotic proto-oncogene in non-Hodgkin's lymphoma cells[8], and it was involved in the t(14;18) chromosomal translocation found in many follicular B – cell lymphoma.[9] Bcl-2 is localized to the luminal cells of the normal breast, which are considered to be the origin of malignant breast disease.[10,11] Bcl-2 blocks apoptosis via the mitochondrial pathway by inhibiting the release of cytochrome C from the mitochondria, thus preventing the cascade of events that results in compromise of the mitochondrial outer membrane potential, which in turn leads to caspase-9 activation and subsequent apoptosis.[4] Bcl-2 has been shown to inhibit chemotherapy-induced apoptosis, and chemotherapy resistance has been reversed in cancer cells treated with Bcl-2-targeting therapy. [12] Although Bcl-2 is an anti-apoptotic protein, high Bcl-2 expression has been observed in ER-positive breast cancer [13, 14] as well as in progesterone receptor (PR)-positive breast cancers [15, 16] and has been associated with improved survival in breast cancer.[17] High Bcl-2 expression has been associated with improved prognosis even among patients at very high risk for distant relapse, with over 10 involved lymph nodes. [4]

Materials and Methods

This cross sectional study included 100 cases of primary breast carcinomas. All specimens were obtained from the archives of pathology laboratory of Rizgary Teaching Hospital and private pathology laboratory in Erbil province during the period from February to November 2013. All cases undergone modified radical mastectomy and all the histological sections, which stained by hematoxylin and eosin were re-examined under light microscope. The data for each patient including age, tumor size, histological grade, stage, axillary lymph node status, histological type, ER and PR status were obtained from database of the pathology reports. The tumors were classified according to the histological classification of the WHO 2003. Tumors staging were done according to TNM staging, (The American Joint Committee on Cancer staging system), 2010. Grading of the tumors was done according to the Nottingham modification of Bloom - Richardson scoring system. The Bcl-2 protein was assessed by immunohistochemical technique. The procedure followed the instructions provided by the manufacturer. The materials for the procedure were obtained from Dakocytomation (Monoclonal Mouse Anti-Human bcl-2 Oncoprotein) Clone: 124 Isotype: IgG1, kappa (code N1587), and the Detection system EnVision G|2 System/AP, Rabbit/ Mouse (code K5007). Scoring of Bcl-2: Positive expression of Bcl-2 gives cytoplasmic staining, positive cells were determined by examining 10 HPF with (400x), the extent of Bcl-2 immunostaining was assessed as follows: [7] Intensity score: (0= none, 1= weak, 2= intermediate, 3= strong). Proportion Score: (0=0%, 1= <10%, 2= 10-50%, 3=51-80%, 4= >80%). Total score= PS×IS (range = 0-12), 0-4 -----› Negative, 6-12› Positive Statistical Analysis Statistical analysis was done by using the Statistical Package of Social Sciences (SPSS) version 19 computer software. Cross tables and association between different variables were measured by using chi-square test. P - Value less than (0.05) associated with these tests was regarded significant. P - Value less than (0.001) was regarded highly significant. Any value more than (0.05) was considered to be non-significant.

https://doi.org/10.56056/amj.2015.08

Results

The clinical and pathological parameters of the patients are shown in the table (1):

Table (1): Clinical and pathological parameters of the patients.

		.No	%
Age	30 - 20	1	1%
	40 - 31	19	19%
	50 - 41	38	38%
	60 - 51	27	27%
	70 - 61	12	12%
	80 - 71	3	3%
Size	(T1 (≤ 2 cm	19	19%
	(T2 (2 – 5cm	72	72%
	(T3 (≥ 5 cm	9	9%
Types	IDC	89	89%
	ILC	6	6%
	Mixed	3	3%
	Others	2	2%
Grade	Grade I	4	4%
	Grade II	71	71%
	Grade III	25	25%
Lymph Nodes	Positive	37	37%
	Negative	63	63%
Vascular invasion	Positive	48	48%
	Negative	52	52%
Estrogen Receptor	Positive	71	71%
	Negative	29	29%
Progesterone Receptor	Positive	59	59%
	Negative	41	41%

The most involved age group was (41-50) by 38% of cases, statistically there was no significant relation between age of patients and Bcl-2 immunoexpression (P value = 0.218) as shown in figure (1). Bcl-2 immunohistochemical stain was expressed in 61% of cases, while 39% of cases show negative immunoreactivity for Bcl-2. The Bcl-2 positivity was expressed by brown cytoplasmic reaction of malignant epithelial cells as shown in figure (2). Normal ductal epithelial cells of the breast and infiltrating lymphocytes were also showed cytoplasmic staining. Statistically there was no significant relation between Bcl-2 immunoexpression and size of tumor (P value = 0.688). From 100 cases of breast cancer 89% of cases were infiltrative ductal carcinoma, Bcl-2 immunoreactivity found in 54 cases of infiltrative ductal carcinoma as shown in table (2), statistically there was no significant relation between histological types of tumor and Bcl-2 immunoexpression (P value = 0.162). 61.9% of cases were grade II as shown in figure (3), statistically there was no significant relation between histological grade of tumor and Bcl-2 immunoexpression (P value = 0.938). From 61% cases of

https://doi.org/10.56056/amj.2015.08

strongly positive Bcl-2 breast carcinoma, 32.8 % cases have positive lymph nodes as shown in figure (4). Statistically there was no significant relation between Bcl-2 immunoexpression and lymph node status of breast carcinoma (P value = 0.190). From 61% cases of positively stained Bcl-2 breast cancer 54.1% of cases has negative vascular invasion as shown in figure (5), statistically there was no significant relation between Bcl-2 immunoexpression and lymphovascular invasion (P value = 0.370). Estrogen receptors were positive in 71% cases of breast carcinoma in which 67.6% of cases showed strong Bcl-2 positive staining as shown in figure (6), statistically there was significant relation between estrogen receptor positivity and Bcl-2 immunoreactivity (P value = 0.030). Progesterone receptors were positive in 59% cases of breast carcinoma in which 74.5% of cases showed strong positive staining for Bcl-2 as shown in Figure (7), statistically there was highly significant relation between Bcl-2 immunoexpression and progesterone receptors (P value =0.001).

Table (2): Relation between Bcl-2 immunoexpression and histological types of breast carcinoma.

		Type				Total
		IDC	ILC	mixed	Others	
Bcl-2	+ve	54	4	3	0	61
	-ve	35	2	0	2	39
Total		89	6	3	2	100

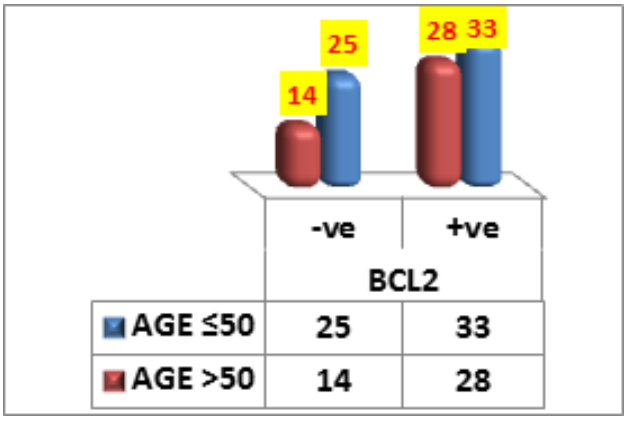

Figure (1): Relation between Bcl-2 Immunoexpression and age of patients

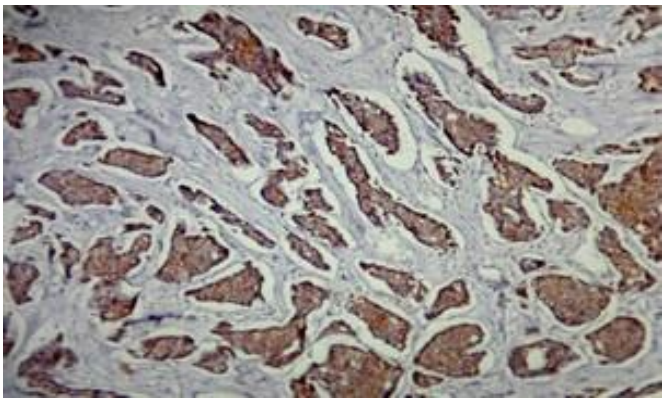

Figure (2): Strong cytoplasmic reaction of Bcl-2 in malignant ductal epithelial cells. X200.

https://doi.org/10.56056/amj.2015.08

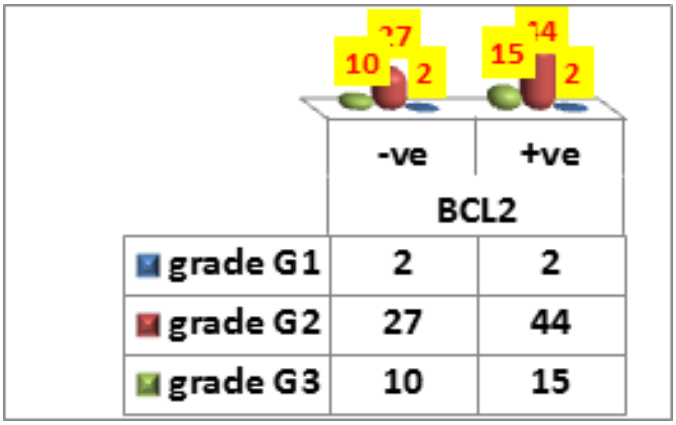

Figure (3): Relation between Bcl-2 immuno metastatic to lymph node, IHC x100

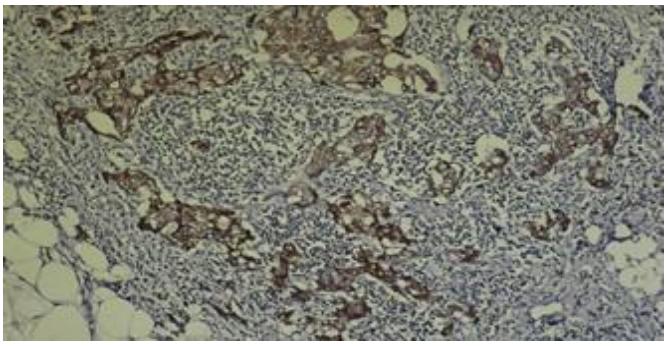

Figure (4): Invasive ductal carcinoma expression and histological grade of carcinoma.

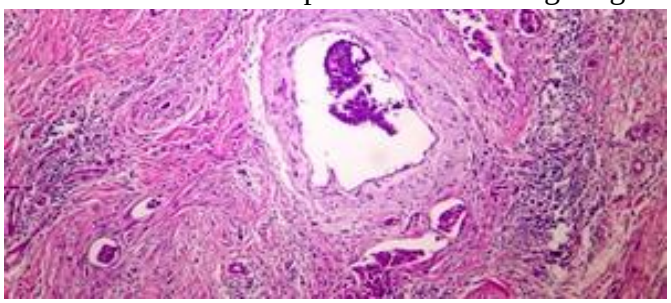

Figure (5): Invasive ductal carcinoma showing lymphovascular invasion (arrows) H&E, x100.

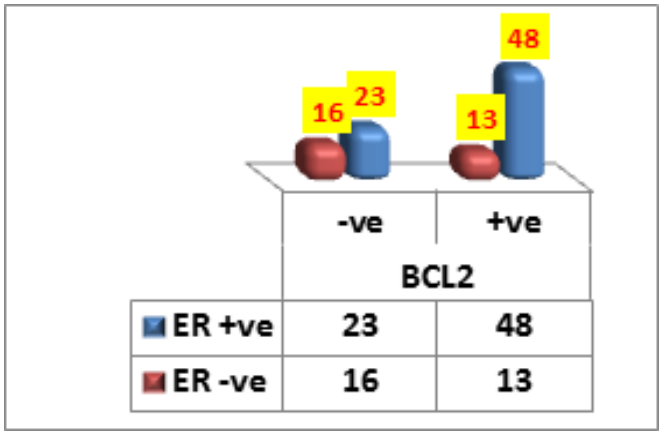

Figure (6): Relation between Bcl-2 immunoexpression and estrogen receptors.

https://doi.org/10.56056/amj.2015.08

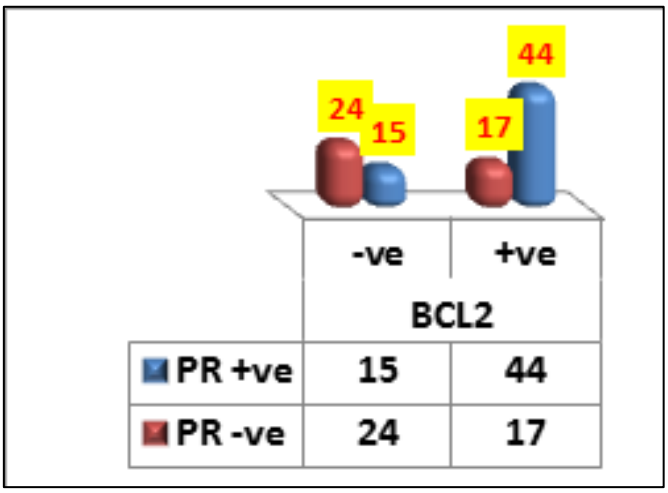

Figure (7): Relation between Bcl-2 immunoexpression and progesterone receptors.

Discussion

One of the major challenges of breast cancer is to de- fine accurate predictive factors that allow the selection of adjuvant therapy which ensures the most benefits and the least harm for the patient. Therefore, various biomarkers are used as a complement to clinicopathological prognostic factors. 18 Among numerous prognostic factors, Bcl-2 was also considered as one of the possible promising markers. Bcl-2 expression in breast cancer is associated with favorable prognostic factor, and it predicts a good outcome in early breast cancer and even in metastatic disease.7 Therefore evaluation of Bcl-2 expression in breast cancer may identify a sub- set of patients with favorable prognosis, who may not benefit from chemotherapy but may benefit from Bcl-2 targeting agents in addition to antihormonal therapy.4 In this study we analyzed the Bcl-2 expression in breast cancer tissue using immunohistochemistry and studied its relationship with clinicopathological parameters and with hormone receptors status (estrogen and progesterone). The age range was 22-75 years with a mean age of 49.5 years, with 38% of cases were in age group 41-50 years, our results were comparable to that reported by Jalal, 201319, Mohamad and Ibrahim, 20097 and Wang et al, 2004 20 . Bcl-2 was expressed in 56.8% of patient below the age of 50 year; this result is analogous to that reported by Abd El-Mageed et al, 2013 18 in which Bcl-2 were more expressed in younger age group less than 50 year. Our study found no significant relation between Bcl-2 immunoexpression and age of patient while Diadone et al, 2003 21 and Andalib et al, 2007 22 found significant direct correlation and they found slight increase of Bcl-2 expression with increase age of the patients. This may be due to the fact that tumors of elderly patients have a more favorable pathobiological phenotype as to be of well differentiated, low proliferative rate and higher ER content compared to those of younger age group.(21) High Bcl-2 expression is associated with small size tumor; this can be explained by inhibitory effect of Bcl-2 on cell proliferation. (23) In this study 72% of cases the tumor size were (2-5)cm in which 62.5% of cases were Bcl-2 positive our result is close to that reported by Cecka et al, 2008 24, Dema et al, 2008 25 , Bilalovic et al, 2004 (26) and Jaafar et al, 2012(27), They found no significant association be- tween Bcl-2 expression and tumor size while Callagy et al, 2006 (3) found a significant association between Bcl-2 expression and tumor size, this difference may be due to large sample size of their study in comparison to small sample size of this study. In this study 89% of cases were infiltrative ductal carcinoma while 11% of cases consist of other subtypes of breast

https://doi.org/10.56056/amj.2015.08

carcinoma, our result is analogous to that reported by Park et al, 2002 (28) and Dema et al, 2008(25) , but the relation between Bcl-2 expression and tumor type failed to reach a significant level, while Mohamad and Ibrahim, 2009(7) and Abd El-Mageed et al, 2013 (18) they found strong correlation between Bcl-2 expression and tumor type, this difference may be due to limited number of cases in the present study. In this study there was a trend for poorly differentiated (grade III) cancers to be Bcl-2 negative (40%) while (61.9%) of grade II cancers showed positive Bcl-2 expression, these results are in agreement to those reported by Park et al, 2002(28) and Dev, 2013(29), other studies found significant inverse association be- tween expression of Bcl-2 and increasing tumor grade. (3, 7) This seems paradoxical because, in experimental models, Bcl-2 overexpression protects cells from apoptotic death and decreases cell-cell adhesion leading to the lost of the contact inhibition. In this way, Bcl-2 is supposed to enhance cancer cells survival and promote tumorogenesis. But, some other studies found that absence of Bcl-2 expression is strongly associated with high proliferation rates and high tumor grade. This suggests the possible role of Bcl-2 in the regulation of cell proliferation.(26) In our study we found no significant association between Bcl-2 immunoexpression and grade of tumor this is in agreement with studies done by Nadler et al, 2008 (4), Bilalovic et al, 2004 (26) and Jaafar et al, 2012.(27) The number of the affected lymph node is the strongest predictive and prognostic factor, yet within the lymph node positive subset and lymph node negative subset of patient there is variability in prognosis. (4,30) Although Bcl-2 positivity detected in 54% of lymph node negative cases, our study found no significant relation between Bcl-2 expression and lymph node status, this result consistent with that re-ported by other studies.(3,4,7,9,17,27,31) However Abd El-Mageed et al, 2013 (18) and Neri et al, 2006(32) in their study found Bcl-2 immunoreactivity significantly correlated with negative axillary lymph node. A study by Hellemans et al, 1995 (17) showed no prognostic significance for Bcl-2 expression in node-negative patients, but Bcl-2 negativity correlated with reduced survival among node-positive patients. The evaluation of Bcl-2 expression and extent of apoptosis may provide useful prognostic information on breast cancer patients; however while increased apoptosis is strongly associ- ated with the progression from primary carcinomas to lymph node metastases; Bcl-2 does not seem to play a significant role in this process.(26) In this study 52% of cases of tumor showed negative lymphovascular invasion in which 63% of them showed strong positivity for Bcl-2 oncoprotein, no significant relation was obtained between Bcl-2 immunoexpression and lymphovascular invasion, this result is in contrast with that reported by Neri et al, 2006(32) and Mohamad and Ibrahim, 2009. (7) The expression of Bcl-2 is a marker of breast cancer with reduced capability of distant colonization even in presence of lymphovascular invasion and this finding may be particularly useful in the clinical setting, allowing to identify a subset of patients with a high risk of relapse who need an intensive therapeutical approach.(33) In this study 67.6% of estrogen receptor positive cases showed Bcl-2 positivity and 74.5% of progesterone receptor positive cases showed Bcl-2 positivity, a significant relation was found between estrogen and progesterone receptors and Bcl-2 expression, this is in agreement with other studies.(3,7,9,17,24,26,27,33,34) This observation confirms the hypothesis that this protein, like PR, is under oestrogen regulation via ER. Binding of estrogen to ER causes its phosphorylation and dimerization followed by transcription of a variety of genes, including secreted growth and angiogenic factors, as well as PR and Bcl-2.(7) In preclinical studies, Bcl-2 protein inhibits apoptosis in vitro and is associated with chemoresistance. For this reason it has

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been hypothesized that Bcl-2 protein overexpression may play a role in the resistance to chemotherapy. (35) In vivo, the expression of Bcl-2 protein should inhibit apoptosis and therefore should mean a worse outcome for the patients. Surprisingly, statistical analysis revealed that Bcl-2 positive patients had better prognosis and better survival, compared with patients with Bcl-2 negative tumors. Several possible explanations for these seemingly paradoxical results have been suggested:

1) Bcl-2 not only inhibits apoptosis, but also has an inhibitory effect on cell proliferation;
2) Bcl-2 expression is regulated by estrogens;
3) Bcl-2 antagonists are present in tumor cells, negating cytoprotective function of Bcl-2. (24) The strong association between Bcl-2, ER, and PR may suggest that cotargeting these molecules in hormone receptor-positive breast cancer might provide greater benefit than chemotherapy, or might play a role as beneficial strategy for sensitizing these tumors to chemotherapy. (4) carcinoma in Erbil. A significant association was observed between Bcl-2 immunoexpression and hormone receptors (ER & PR). The Bcl-2 immunoexpression has no relation with the age of patients, size, type and grade of the tumor, lymphovascular invasion and axillary lymph node metastasis

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