(International Print/Online Journal)

SJIF IMPACT FACTOR: 4.617
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 2, Issue 5, Page No: 173-181
September-October 2019

IJMSCR

ROLE OF BCL-2 IN ORAL SQUAMOUS CELL CARCINOMA: A SYSTEMATIC REVIEW

[1]Dr. Jaya Singh, [2]Dr. Shruti Singh, [3]Dr. Mohd Saleem, [4]Dr. Jinkimoni Singha, [5]Dr. Pritha Chowdhury, [6]Dr. Neelam Lodhi

[1,2]Senior Resident, [3]Ex Senior Resident, [4,5]Private Practitioner

[1, 2,3]Department of Oral Pathology and Microbiology, Faculty of Dental Sciences, KGMU, Lucknow

[4]MDS, Private Practitioner, Assam, [5]MDS, Private Practitioner, Kharagpur

[6]MDS, Apollo White Dental Clinic, Bangalore

Corresponding Author

Dr. Jaya Singh- Senior Resident,

Department of Oral Pathology and Microbiology, Faculty of Dental Sciences, KGMU, Lucknow

Type of Publication: Original Research Paper

Conflicts of Interest: Nil

ABSTRACT

Oral Squamous Cell Carcinoma (OSCC) is a major public health issue all around the world. Proliferation, differentiation and apoptosis are fundamental aspects of tumor biology. Various studies on oral carcinogenesis showed that this process may involve not only increased cell proliferation but also decreased cell death or apoptosis or increased cell-survival. There were genetic alterations in the molecules that play a crucial role during apoptosis. Anti-apoptotic proteins like Bcl-2 gene family and inhibitors of apoptosis (IAP) gene can play a major role in oral carcinogenesis. The current review comprehensively studied the role of Bcl-2 in oral carcinogenesis and thereby check if it can act as target molecule in cancer therapy.

Keywords: NIL.

INTRODUCTION

Head-and-neck squamous cell carcinomas (HNSCCs) are among the most destructive of tumors, with OSCC representing the majority. More than 11 million people are diagnosed with cancer every year with an estimation of 16 million new cases every year by 2020. The tendency for local and regional metastases owing to the close proximity and uninhibited infiltration of local lymph nodes is high, and this is thought to be the greatest contributor to the morbidity and mortality associated with OSCC. Five-year survival rates are reportedly as low as 9% for some parts of the oral cavity, largely due to late-stage diagnosis when tumor, node, metastasis Stage IV has occurred. [1]

In India alone, 2.5 lakh new patients are diagnosed with HNSCC. The prognosis depends on various factors such as patient's age, size, site, thickness, degree of differentiation and spread into regional lymph nodes. [2]

Survival significantly surges between 66% and 85% when OSCC is detected and treated before lymph node infiltration. Early detection also improves morbidity accompanying the treatment of OSCC, with late-stage diagnosis associated with poorer prognosis. Although it has not been previously reported, it follows that diagnosis and management at the "precancerous" stage would further improve survival rates. [1] Despite the recent advances in diagnostic techniques and improvements in treatment modalities, the 5-year survival rate has not been improved for 30 years. [3]

Proliferation, differentiation and apoptosis are fundamental aspects of tumor biology. Various studies on oral carcinogenesis showed that this process may involve not only increased cell proliferation but also decreased cell death or apoptosis or increased cell-survival. So, there is mounting evidence which suggests that there were genetic alterations in the molecules that play a crucial role during apoptosis. Altered expression of these genes will cause dysregulation of this process.[4,5]Anti-apoptotic proteins like Bcl-2 gene family and

inhibitors of apoptosis (IAP) gene family are one among them which play a crucial role in oral carcinogenesis thereby they can act as target molecules in cancer therapy.

Bcl-2 is a proto-oncogene first noticed in human B-cell follicular lymphoma with chromosomal translocation t (14; 18) (q 32; q 21).It encodesa 26-kDa Bcl-2 oncoprotein localized to outer mitochondrial membrane, endoplasmic reticulum and nuclear envelope.[5] Bcl-2 oncoprotein is demonstrated in normal tissues, including oral epithelium and it is topographically restricted to cells in proliferating zones and cells with long-lifespans.[6]

In human solid tumors, Bcl-2 is described in a wide variety of cancers including head and neck carcinoma[8] and oral carcinoma.[9] Bcl-2 has gained a unique importance as inhibitor of apoptosis by keeping the cells alive and thereby giving way to the action of various carcinogens and viral agents and interaction with other genes which aids in progression to neoplasia. Many authors have shown increased expression of Bcl-2 oncoprotein in earlyphase of oral carcinogenesis leading to apoptosis impairment.[10] Hence expression of Bcl-2 oncoprotein in oral cancer could be a considered as a molecular marker for early diagnosis, progression and prognosis. It was also a therapeutic target for cytotoxic anti-cancer drugs.

ROLE OF Bcl-2 IN TUMORIGENESIS:

Bcl-2 proto-oncogene blocks a distal step in an evolutionary conserved pathway of apoptosis. Its abnormal expression, usually in terms of overexpression in genetically modified cells such as tumor cells, contributes to the expansion of the damaged cell clone by preventing cell turnover due to programmed cell death, leading to cellular immortalization. By promoting cell survival, Bcl-2 facilitates the permanent acquisition of mutations and malignant transformation. Moreover, increased Bcl-2 expression in cancer cells possibly reflects tumor cell resistance to apoptosis and may have implications for the irresponsiveness to treatments.[11]

The relationship between Bax and Bcl-2 is probably regulated by the non-mutant form of tumor suppressor gene p53. By down regulating Bcl-2 orup regulating Bax, wild type p53 promotes cell death. A mutant p53 may accompany an up regulation in Bcl-2 and down regulation in Bax which inhibits the cell death and promotes cell survival.[12] Expression of Bcl-2 in various neoplastic tissues such as lymphoma, prostatic carcinoma, breast carcinoma, endometrial carcinoma, melanoma, gastrointestinal carcinoma, transitional carcinoma, SCC of lung, squamous cell carcinoma of skin, SCC of cervix, basal cell carcinoma, Nasopharyngeal carcinoma and OSCC.[13]

METHOD OF COLLECTION OF DATA:

Literature was searched for key words “HNSCC, OSCC, Bcl-2, epithelial tumors, apoptosis” to include articles published on various studies conducted on Bcl-2 in Oral squamous cell carcinomas in different databases such as PubMed, Embase and Liliacs etc. Only original research which studied correlation of Bcl-2 and OSCC were included in this study. Review articles and studies with insufficient data were excluded. The search yielded 87 relevant articles that had information on hCG-β in epithelial tumors. Only 23 articles were selected based on our inclusion and exclusion criteria; remaining 64 articles were excluded.

Inclusion criteria: Only original research pertaining to Bcl-2, OSCC and OPMD’s were considered.

Exclusion criteria: Case reports and review articles were excluded.

Bcl-2 EXPRESSION IN NORMAL TISSUES:

Bcl-2 is expressed in a wide variety of fetal tissues. Bcl-2 has been found to be strongly expressed during the embryonic and early postnatal period. Bcl-2 protein expression is mainly observed in cell populations with a long life and/ or proliferating ability such as duct cells in exocrine glands, basal keratinocytes, cells at the bottom of colon crypts and neurons. In the skin of both adult and embryo and also embryonic kidney and cartilage, Bcl-2 expression was in cells which were undergoing morphological transition from undifferentiated stem cells to committed precursor cells.[14]

Bcl-2 EXPRESSION IN ORAL SQUAMOUS CELL CARCINOMA

Jordan RCK et al had conducted a study to know differential expression of Bcl-2 and Bax in OSCC. The expression of Bcl-2 was identified in 18 cases and its expression was strongest in 86% of PDSCC (poorly differentiated oral squamous cell carcinoma).

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Bax immunoreactivity was strongest in 72% of WDSCC (well differentiated oral squamous cell carcinoma). These results suggest that alterations of Bcl-2 and Bax may play a role in the progression of OSCC.[15]

Baldev B. Singh et al evaluated an expression of Bcl-2 in oral dysplasia and oral squamous cell carcinoma. 28 out of 75 cases showed Bcl-2 immunopositivity. Cases of severe dysplasia showed more positivity than moderate and mild dysplasia. Bcl-2 expression was positive in 15 out 60 OSCC cases. PDSCC showed more positivity than WDSCC. This deregulated expression of Bcl-2 oncoprotein in pre-cancerous and cancerous lesions suggests a possible role in the advancement of oral cancer.[13]

Lado Lako Loro et al that there is an association between decreased Bcl-2/ Bax expression ratio and increased apoptosis in OSCC. In normal oral mucosa, Bcl-2 was expressed in both basal (97%) and supra-basal layers (91%). In OSCC, there was a marked reduction of Bcl-2 positive cells in the basal part and in central part ofWDSCC (33%) and MDSCC (6.1%) and also PDSCC (1.9%). More cells expressed Bax in the supra-basal layer of Oral epithelium (65%) and central parts of OSCC than in the basal layer of OE (19%) and basal parts of OSCC. Higher proportion of cells expressed bax in the central part of WDSCC than PDSCC. They concluded that, in OSCC compared to OE there is a decreased Bcl-2 expression ratio and increased apoptosis.[16]

Tanuja Teni et al determined the expression of Bcl-2 and Bax in 63 oral cancers and 31 premalignant lesions. Their study revealed over expression of tumor specific cytoplasmic Bcl-2 in 56% oral cancers and in 16% oral lesions comprising leukoplakia and OSMF, whereas Bax expression was identified in 43% oral cancers and 55% oral lesions. This study concludes that overexpression of apoptosis regulators Bcl-2 and Bax in oral cancers represents the early events in oral carcinogenesis.[17]

Saikrishana P et al evaluated the expression of Bcl-2 oncoprotein in different grades of OSCC. 9 cases of WDSCC and 3 cases of MDSCC showed Bcl-2 positivity. This study concludes Bcl-2 prolongs cell survival in epithelial cells and thereby giving way to other external stimulus like action of carcinogens and viral agents and interaction with other genes and aids in progression to neoplasia.[12]

Mariola Sulkowski et al reported a study on correlation between Bcl-2 protein expression and some clinicopathological features of OSCC. This study included surgically treated 129 patients of OSCC. Results were statistically significant between Bcl-2 expression of OSCC and higher tumor grading, higher mitotic index, higher index of atypical mitosis as well as micro focal pattern of tumor invasive margin.[18]

L L Loro et al investigated whether Bcl-2 loss in oral epithelial dysplasia (OED) and OSCC, and BAX loss in PDSCC could be accredited to mutations. Bcl-2 and Bax mutations were not detected in their study. Downregulation of Bcl-2 in OED and OSCC may be the result of transcriptional regulation.[19]

Popovic B et al estimated immunohistochemical expression of Bcl-2 in OSCC and the reactivity was scored according to the intensity and percentage of Bcl-2 positive cytoplasmic cells. Positively stained Bcl-2 cells were less. Low level of Bcl-2 expression in the sample seems to be associated with higher survival rate. They concluded that a valuable predictor of tumor behavior and disease outcome can be correlated with the level of Bcl-2 expression.[20]

Suri et al evaluated the expression of Bcl-2 in different histological grades of OSCC. In this study all 38 cases showed Bcl-2 positivity. More no. of positive cells is in PDSCC than in WDSSC. The intensity of Bcl-2 expression was more in MDSCC, while in PDSCC showed light and dark intensity. When the distribution pattern of Bcl-2 expression was assessed, the tumor islands devoid of central keratinization and showed Bcl-2 expression in all the tumor cells. This concludes that the no. of Bcl-2 positive cells was increased from WDSCC to PDSCC.[21]

S Carnelio et al assessed the tumor behavior using TMA technology based on the expression of p53, Bcl-2 and E-cadherin. Bcl-2 was the most frequently expressed biomarker. They saw that the expression of Bcl-2 was inversely related to the degree of differentiation. They concluded that the molecular data obtained from TMA will enhance diagnosis, provide better prognosis and will improve cancer treatment for individual patients.[22]

Coutinho-Camillo C M et al conducted a study to evaluate and correlate the expression of promotor and

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inhibitor apoptotic proteins with clinicopathological features of OSCC. Their result showed the association of the Bcl-2 family in pathogenesis of OSCC and suggest that the expression of apoptotic molecules might be used as a prognostic marker for OSCC.[23]

Sudha V M et al described the role of Bcl-2 in oral potentially malignant disorders and OSCC. Of 30 OSCC cases, 11 cases showed greater supra basal keratinocyte staining. 15 cases showed positivity in the basal cell layer, with a smaller number of supra-basal cells positivity and rest of 4 cases did not show positivity. 8 cases of leukoplakia, 6 cases of OSMF, 6 cases of OLP showed greater basal cell staining. They concluded that a definite number of cases showed bcl-2 over expression, but a greater number of studies need to be done to come to a definite conclusion.[24]

Resmi G Nair et al determined Bcl-2 expression in severe epithelial dysplasia and in different histological grades of OSCC. Out of 10 cases in epithelial dysplasia, 8 cases exhibited intense expression and 2 cases exhibited moderate expression. Among all grades of OSCC, PDSCC showed intense reactivity than WDSCC and MDSCC. This study concludes that overexpression of Bcl-2 oncoprotein was seen in severe epithelial dysplasia involving the entire thickness with its down regulation in differentiating carcinomas, suggesting the role in early stages of tumor progression.[25]

A Sri Kennath J Arul et al examined Bcl-2 and Ki-67 expression in varying histological grades of OSCC. Bcl-2 positivity was observed in all cases, while its expression was decreased from WDSCC to MDSCC to PDSCC. MIB-1 positivity was observed in all cases. No. of MIB-1 positive cells increased from WDSCC to MDSCC to PDSCC. This study concludes that anti-apoptosis was dominant in well differentiated lesions than in moderately and poorly differentiated lesions; while cell proliferation dominated in poorly differentiated lesions than moderately and well differentiated lesions.[26]

Rahmani et al examined the impact of PTEN and Bcl-2 in the pathogenesis of OSCC and noticed agradual loss of PTEN expression in OSCC. The overexpression of Bcl-2 and loss of PTEN expression were correlated to PDSCC. Thus, they concluded that alteration of PTEN and Bcl-2 is likely an important molecular event in pathogenesis of oral carcinoma.[27]

Shima Nafarzadeh et al evaluated Bax and Bcl-2 expression in oral lichen planus (OLP) and OSCC. There was no significant difference in bax expression between OLP-E and OLP-R and also between OLP and WDSCC. Expression of Bax in OLP was significantly higher than normal mucosa. 4 out of 11 cases of WDSCC cases expressed Bcl-2. No Bcl-2 expression was seen in OLP and normal mucosa.[28]

Jessica Garewal et al conducted a study on expression of Bcl-2 and MIB-1 in OSCC. MIB-1 which is a proliferative marker showed expression prevalent was WDSCC and PDSCC. Bcl-2 expression is predominant in WDSCC to MDSCC to PDSCC and concluded that apoptosis plays a key role in the initial stages of carcinogenesis.[29]

Paramee Thongsuksai et al checked the expression of p16, p53, Bcl-2, and Bax in patients with OSCC and OPSCC (Oro-pharyngeal squamous cell carcinoma). The frequencies of p16, p53, Bcl-2, and Bax expression in OSCC were 13%, 45%, 4%, and 66%, and in OPSCC were 18%, 53%, 22%, and 75%, respectively. The expression pattern of p16, p53, Bcl-2, and Bax were similar in OSCC and OPSCC with Bax having a prognostic significance for both the tumor sites.[30]

Suni Ann Thomas et al also studied the expression of Bcl-2, Bax and p53. In this study they observed overexpression of p53 and Bcl-2 and decreased expression of Bax in patients with OSCC and concluded that alteration in apoptosis can be accounted for oral carcinogenesis.[31]

Juneja S et al evaluated the expression of Bcl-2 in OED and OSCC. Immunostaining of Bcl-2 was identified in basal and parabasal layers in OED. In OSCC, Bcl-2 expression was prominent in the peripheral cells of the infiltrating tumor islands which diminished towards the center in WDSCC and MDSCC, whereas stronger and more diffuse expression of Bcl-2 oncoprotein was seen in PDSCC.[32]

Pavithra V et al evaluated the correlation of Bcl-2 expression in OSCC patients with lymph node metastasis and without metastasis. No significant difference in the expression of Bcl-2 was seen between the study groups. Apoptosis is regulated by

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interaction among the Bcl-2 gene family. Hence, they suggested that the evaluation of Bcl-2 along with other apoptotic proteins could be of help in defining their role in pathogenesis and prognosis of metastatic and non-metastatic OSCC.[33]

Ipshita B et al conducted a study to check the expression of *p53*, Ki-67 and *Bcl-2* in patients with OED and OSCC patients. A statistically significant increase for Ki-67 expression was seen in OSCC cases than in OED while the expression of *p53* was also similar, but it was statistically insignificant. Also, they found no definite association between *Bcl-2* and the percentage of immunopositive cells and the grade of malignancy.[34]

Pallavi et al assessed the expression of Bcl-2 and c-Myc in OED and OSCC. They concluded that variable expression of c-Myc and Bcl-2 reveals that these proteins act in concordance in early stages of carcinogenesis, whereas in later stages, due to the reduced activity of Bcl-2, c-Myc interacts in coordination with other oncogenes contributing to tumor progression.[35]

CONCLUSION

Bcl-2 protein is one of the most assuring anti-apoptotic proteins expressed in OPMD's and OSCC. Most of the articles reviewed in this research suggested that the expression of Bcl-2 might be used as a prognostic indicator for OSCC. A significant role of Bcl-2 in cancer development was deciphered. Numerous inhibitors and promotors of apoptosis have been found which could be used in diagnosing and hence treating oral cancer. Therefore, analysis of Bcl-2 should be done for diagnosing OPMD's and OSCC so that early intervention is possible, and thus improving the treatment outcome and patient survival.

S. no.	Name	Year	Study Design	Tissue	Sample size	Relevance
1.	Jordan R C K et al	1996	Differential immunostaining of Bcl- 2 and Bax in OSCC	OSCC	n=30	Alterations of bcl-2 and bax may play a role in the development of OSCC.
2.	Baldev B Singh et al	1998	Immunohistochemical expression of Bcl- 2 in OED and OSCC	OED & OSCC	n=135	Deregulated expression of Bcl-2 oncoprotein in precancer and cancer suggests a possible role in the advancement of oral cancer.
3.	Lado Lako Loro et al	1999	Immunohistochemical expression of frozen section to check Bcl-2/ Bax expression ratio	OE & OSCC	n=23	There is a decreased Bcl-2 expression ratio and increased apoptosis in OSCC compared with OE.
4.	Tanuja T et al	2002	Immunohistochemical expression of bcl-2 and bax	OSCC & premalignant lesions	n=94	An aberrant bcl-2 expression was observed.
5.	Saikrishana P et al	2002	Expression of Bcl-2 oncoprotein in different grades of OSCC	Different grades of OSCC	n= 67	They concluded that Bcl-2 prolongs cell survival in epithelial cells aids in progression to neoplasia.

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6.	Mariola Sulkowski et al	2003	Correlation between Bcl-2 protein and some clinicopathological features of OSCC	OSCC	n=129	Positive Bcl-2 expression may contribute to unfavorable histopathology of OSCC.
7.	L L Loro et al	2005	Whether loss of Bcl-2 loss in OED and OSCC, and BAX loss in PDSCC by IHC and in situ hybridisation could be accredited to mutations	OED & OSCC	n=50	No mutations were found that could explain loss of BCL-2 in oral dysplasia and carcinoma. Downregulation of BCL-2 in OED and OSCC may be the result of transcriptional regulation.
8.	Popovic B et al	2007	IHC level of bcl-2 proteins in OSCC	OSCC	n=26	Low percent of positively stained cells were seen which could confer a higher survival rate.
9.	Suri et al	2009	Bcl-2 expression in grades of OSCC.	OSCC	n=38	Number of positive Bcl-2 cells increased with the increasing grades of OSCC.
10.	Carnelio S et al	2010	Expression of p53, Bcl-2 and E-cadherin using TMA technology	OSCC	n= 30	The expression of Bcl-2 was inversely related to the degree of differentiation.
11.	Coutinho-Camillo C M et al	2010	Correlation and expression of promotor and inhibitor apoptotic proteins with clinicopathological features of OSCC	OSCC	n=29	The expression of apoptotic molecules might be used as a prognostic indicator for OSCC
12.	Sudha V M et al	2011	Immunohistochemical expression of Bcl- 2 in OPMD and OSCC	OPMD and OSCC	n=60	Role of bcl-2 in the development and progression of oral neoplasia was confirmed.
13.	Resmi G Nair et al	2011	Immunohistochemical expression of Bcl- 2 in severe dysplasia	Severe dysplasia and grades of	n=40	Suggested the role of Bcl-2 in early stages of tumor progression

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			and OSCC	OSCC		
14.	A Sri Kennath J Arul et al	2011	Expression of Bcl-2 and Ki-67 in grades of oral cancer	OSCC	n=30	They concluded that anti-apoptosis was dominant in well differentiated lesions while cell proliferation dominated in poorly differentiated lesions
15.	Rahmani et al	2012	Impact of PTEN and Bcl2 in the genesis of OSCC	OSCC and Inflammatory lesion	n=75	They concluded that alteration of PTEN and Bcl-2 is likely an important molecular event in genesis of oral carcinoma.
16.	Shima Nafarzadeh et al	2013	Immunohistochemical staining method for evaluating bax and bcl-2 expression in epithelial layers.	OSCC and OLP	n=61	Expression was seen only in carcinoma cases and thus concluding the reduced malignant potential of OLP
17.	Jessica Garewal et al	2014	Studied the expression of Bcl-2 and MIB-1 in OSCC	OSCC	n=30	Both Bcl-2 and MIB-1showed more positivity in WDSCC as compared to PDSCC.
18.	Paramee Thongsuksai et al	2014	Expression of p16, p53, Bcl-2, and Bax in oral and oropharyngeal carcinoma.	OSCC and OPSCC	n=277	Bax expression had prognostic significance for both tumor sites.
19.	Thomas S A et al	2014	Immunohistochemical expression of Bcl-2, Bax and p53 in oral carcinoma.	OSCC	n=26	They concluded that apoptotic mechanism is dysregulated in oral carcinogenesis.
20.	Juneja S et al	2015	Immunostaining of Bcl-2 in oral premalignant and malignant lesions.	OED and OSCC	n=60	They observed stronger and more diffuse expression of Bcl-2 oncoprotein was seen in poorly differentiated OSCC.
21.	Pavithra V et al	2017	Immunohistochemical expression of Bcl-2 in OSCC with and without nodal metastasis.	OSCC	n=30	They concluded that these proteins could define a role in pathogenesis of OSCC.
22.	Ipshita B et al	2017	Comparison and Immunoexpression of	Leukoplakia and OSCC	n=60	P53 and Ki-67 showed increased expression but

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			p53, Ki-67 and Bcl-2 in leukoplakia and OSCC.			insignificant difference amongst the groups. Also, no significant difference of Bcl-2 expression was noted in the grades of malignancy.
23.	Pallavi et al	2018	Assessed the expression of Bcl-2 and c-Myc in OED and OSCC.	OED and OSCC	n=70	They saw and concluded that due to the reduced activity of Bcl-2, c-Myc interacts in coordination with other oncogenes contributing to tumor progression.

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