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STUDY OF EXPRESSION OF HER2/NEU RECEPTOR IN GALLBLADDER CARCINOMA AND ITS ASSOCIATION WITH CLINICOPATHOLOGICAL PARAMETERS - AN INSTITUTIONAL EXPERIENCE FROM NORTH EAST INDIA

Oncopathology

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ABSTRACT

Background: Gall bladder carcinoma (GBC) is an aggressive malignancy with high mortality and aggressive course, with palliation as the only available option. It is the most common biliary tract malignancy found worldwide with very high incidence in North India. It is characterized by poor prognosis and ineffective treatment especially in advanced stage. The aim of this study was to evaluate HER2/neu immunoexpression in advanced GBC patients and to correlate it with the clinicopathological parameters so as to identify GBC patients who can benefit from targeted therapy. **Methods:** The study was conducted in the Department of Oncopathology, State Cancer Institute, Guwahati, Assam. A total of 25 cases of advanced GBC were evaluated for immunohistochemical expression of HER2/neu. Clinicopathological parameters of GBC were studied and correlated with immunoexpression of HER2 /neu. **Result:** The mean age of the GBC patients was 55.4 years with female predominance. On histopathology, majority cases were conventional adenocarcinoma. The expression of HER2/neu was positive in 4/25 cases (16%). It was significantly more positive in well to moderately differentiated gall bladder carcinoma (P<0.05). Majority of these cases were ≤grade 2 and in advanced stage. **Conclusion:** Among GBC patients, HER2/neu expression was 16%. Significant HER2/neu expression was seen in well to moderately differentiated gall bladder carcinomas. HER2/neu can be used as predictive and prognostic markers respectively, with rationale to further explore the use of anti-HER2 therapy in gall bladder cancer.

KEYWORDS

Gall bladder carcinoma; HER-2/neu; gall bladder adenocarcinoma; immunohistochemistry.

INTRODUCTION:

Gallbladder carcinoma (GBC) is one of the most common and aggressive biliary tract malignancy found worldwide.[1] It accounts for 1.2% of all new cancer related cases and 1.7% of all cancer related deaths worldwide.[2] Its incidence is higher in the Indian subcontinent, mainly in the northern and eastern regions, accounting for 80 to 95% of cases[3]. Overexpression of Her2/Neu is associated with poor prognosis in breast and gastric carcinomas, which is also being studied for GBC.[4] The role of HER2/neu expression in gallbladder cancer and targeting this receptor in the management of gallbladder cancer has also been an area of recent research. There are very few reports in the literature especially in the Indian context regarding HER2/neu expression in gallbladder carcinoma (GBC).[1] Regarding prognostic role of HER-2/neu, some authors have found significant correlation of HER-2/neu overexpression with tumor grade and patient survival while few failed to establish any significant correlation.[5,6]

Aims And Objectives:

To study the expression of Her2/neu by immunohistochemistry in GBC and to correlate it with the clinicopathological parameters so as to understand their relation to prognosis, paving the way for targeted therapies for better treatment outcomes and patient survival.

Methods And Methodology:

This is a cross-sectional study conducted at State Cancer Institute, Guwahati, Assam for a 2 year period from January 2023 to December 2024. A total of 25 cases of GBC with metastasis were evaluated. After the preliminary study of all Hematoxylin and Eosin stained sections, histopathological parameters namely tumor grade, tumor differentiation, perineural/ lymphovascular invasion, lymph nodal status, pathological stage as per AJCC of all the GBC cases were evaluated and tabulated on a pre-structured performa. IHC staining was done. The relative frequency of Her2/neu positivity was scored and correlated with other histological prognostic parameters of the tumor. Controls were taken from the known cases of the breast specimen. An approval for this study was obtained from the Institutional Ethical Committee.

Immunohistochemical Evaluation:

Cell membrane staining was used to assess positivity. HER2/neu positivity was defined according to the CAP/ASCO (College of American Pathologists/American Society of Clinical Oncology) criteria for breast cancer, given their wide acceptance in scientific literature. Immuno-staining classification was based on staining intensity & percentage of stained cells.[7]

Interpretation And Immuno-scoring:

IHC 0: No reactivity or membrane reactivity in < 10% of tumour cells.
IHC 1+: Faint/ barely perceptible membrane reactivity in ≥ 10% of tumour cells, cells are reactive only in part of their membrane.
IHC 2+: Weak to moderate complete, basolateral, or lateral membrane reactivity in ≥ 10% of tumour cells.
IHC 3+: Strong complete, basolateral, or lateral membrane reactivity in ≥ 10% of tumour cells.

RESULTS:

There were approximately 120 cases of cholecystectomy done for GBC at our institute in last 2 years, out of which IHC for HER2neu was done in 25 cases of GBC with metastasis. The age of patient ranged from 42 to 67 yrs and mean age was 55.4 years, with female predominance.The presenting symptoms were commonly pain in right upper abdomen. The most common radiological finding was wall thickening. Most common histology was adenocarcinoma, most of which were moderately differentiated. The most common tumor site was fundus of gall bladder. Maximum cases in our study were in stage T3. HER-2/neu overexpression was seen in 16% (4/25). Majority of these cases were of well to moderately differentiated type, ≤ grade 2 and in advanced stage with lymph node metastasis in 4 cases and LVI and PNI in 3 cases each.

Table 1: Correlation of HER-2/neu status with clinicopathological parameters

Parameters		3+	2+	1+	Neg	P value
Gender	Male	0	0	1	1	0.7865
	Female	4	1	5	13	
Age range	≤50 yrs	1	1	1	5	0.3991
	>50 yrs	3	0	5	9	
Tumor Type	WD Adenocarcinoma	2	0	0	7	0.0207
	MD Adenocarcinoma	2	0	6	5	
	PD Adenocarcinoma	0	0	0	1	

	Adenosquamouscarcinoma	0	1	0	1	
Tumor stage	≤ T2	1	1	3	5	0.5256
	≥ T3	3	0	3	9	
Tumor size	< 3 cm	1	0	2	7	0.6795
	3 to ≤5 cm	2	1	4	6	
	>5 cm	1	0	0	1	
Tumor site	Neck	0	1	2	3	0.2588
	Fundus	3	0	1	8	
	Body	1	0	3	3	
Serum Markers	Normal	1	0	2	5	0.8839
	Increased	3	1	4	9	

Table 2: Correlation of HER-2/neu status with LVI, PNI, LN, Metastasis

Parameters	3+	2+	1+	Neg
Lymphovascular Invasion	3	0	3	6
Perineural Invasion	3	0	3	8
Lymph nodal involvement	4	1	4	8
Metastasis	1	0	4	7

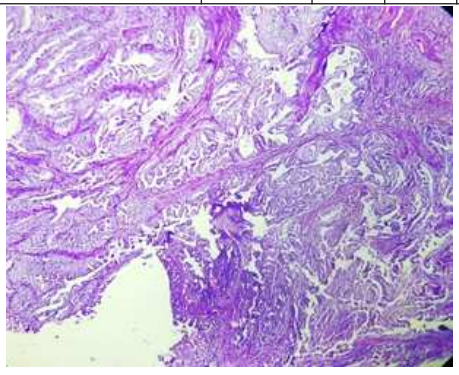

Fig (a): HPE image showing well differentiated adenocarcinoma of gallbladder

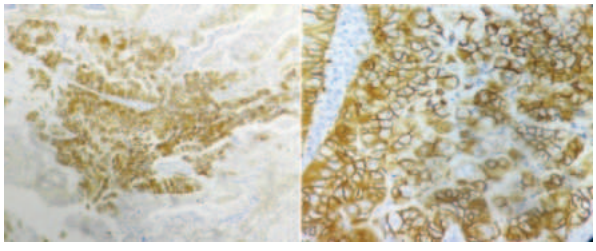

Fig (b): Low power view showing positive HER2 neu staining, (c): High power view showing strong complete, basolateral, or lateral membrane reactivity in ≥ 10% of tumour cells (Score 3+)

DISCUSSION

HER-2/NEU, a protein mostly present at the surface epithelium of large and septal bile ducts, is encoded by ERBB2 gene in humans. Overexpression of this gene product, which occurs in about one-fourth to two-thirds of the biliary tract carcinomas, may be used as a phenotypic marker for neoplastic transformation with a poor prognosis. [3] Expression of HER2/neu has been intensively studied in different tumor entities and has led to the use of targeted therapy with specific inhibitors or antibodies of these receptors in colorectal, breast, stomach, lung as well as head and neck cancer. Its expression as potential therapeutic targets has been reported in various tumors. [8]

The pathogenic role of Her-2 in the development of GBC is not well established in humans.[9] A study conducted by Kiguchi et al., demonstrated over-expression of Her-2 in biliary epithelium leading to the development of GBC. [10] Kiguchi et al., studied on transgenic mice and suggested that targeting both the EGFR and erbB2 (Her-2) may be an effective strategy for the treatment of GBC.[11] Pignochino et al., demonstrated that the Her-2 pathway is suitable therapeutic targets for biliary tract cancers. [12] In yet another study, Milind Javle et al., are of the view that Her-2 blockade is a promising treatment strategy for gallbladder cancer patients with gene amplification and deserves further exploration in a multi-center study. [13] A phase II clinical trial was performed by the National Cancer Institute, the USA, from May 2007 to November 2011 to determine the efficacy of trastuzumab in GBC. This trial included only four patients and showed poor results as three patients showed progressive disease. [14] However, in the above trial, trastuzumab was used as a single agent without any neoadjuvant therapy.

For biliary tract carcinoma, data for HER2/neu over-expression have been presented in mostly small patient cohorts. Only few studies of over-expression of Her2/neu in gallbladder cancer have been reported from India. Also equivocal IHC staining (2+) cases are an important part of the ongoing discussion. Next to IHC staining to evaluate Her2/neu protein over-expression, a second line gene amplification test is generally deemed necessary for these cases. [8]

In our study, the mean age was 55.4 years, with female predominance which correlated with other studies.[1,2,4] The expression of HER2/ neu was positive in 4/25 cases. It was significantly more positive in well and moderately differentiated gall bladder carcinoma (P<0.05), which correlated with other studies. [1,2,3]

Therefore, in this study, we have attempted to identify the immune expression of HER-2 in 25 patients with GBC, assessing their correlation with the various clinicopathological parameters to understand their role in targeted therapy and significance in prognosis. HER2/neu expression was seen in well and moderately differentiated gall bladder carcinomas, thus providing rationale to further explore the use of anti-HER2/neu therapy in gallbladder cancer.

CONCLUSION:

Her2/neu expression in GBC occurs especially in advanced stage disease and its therapeutic targeting seems promising. Therefore, they may serve as independent prognostic factors and also as targets for molecular therapy in GBCs and offer a survival benefit.

REFERENCES:

1. InaraAbeer et al. EGFR and HER2neu Expression in Gall Bladder Carcinoma and Its Association with Clinicopathological Parameters - An Institutional Experience from North India. DOI:10.31557/APJCB.2021.6.1.57
2. Pragya Jain et al. HER-2/neu over expression in gall bladder adenocarcinoma: A quest for potential therapeutic target. DOI: 10.4103/IJPM.IJPM_664_19
3. Chhanda Das et al. Role of EGFR and HER-2/NEU Expression in Gall Bladder Carcinoma (GBC). DOI https://doi.org/ 10.1055/s-0041-1726563 ISSN 0974-2727.
4. N. Singh1 et al. Expression of Her2/Neu and Ki-67 proliferation index in gall bladder carcinomas: Clinicopathological significance. https://doi.org/10.1016/j.annonc.2022.09.117
5. Chaube A, Tewari M, Garbyal RS, Singh U, Shukla HS. Preliminary study of p53 and c-erbB2 expression in gall bladder cancer in Indian patients. BMC Cancer 2006;6:126.
6. Doval DC, Azam S, Sinha R, Batra U, Mehta A. Expression of epidermal growth factor receptor, p53, Bcl2, vascular endothelial growth factor, cyclooxygenase-2, cyclin D1, human epidermal receptor-2 and Ki-67: Association with clinicopathological profiles and outcomes in gallbladder carcinoma. J Carcinog 2014;13:10.
7. Wolff AC et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Journal of Clinical Oncology. 2018 07 10;36(20):2105-2122. https:// doi.org/10.1200/jco.2018.77.8738.
8. Ashai F, Ashraf A, Rashid A, Banday BM, Bhalla S, Dhawan S. Expression of Her2/neu receptor in carcinoma gallbladder correlates significantly with advanced tumor stage. Int J Hepatobiliary Pancreat Dis 2015;5:86–91.
9. Zafar G, Afzal S, Zafar A, Zaman S. Gallbladder Adenocarcinoma, Potential Target for Anti-Her-2 Therapy. Acta Med Iran. 2020;58(5):234-239.
10. Kiguchi K, Carbajal S, Chan K, Beltrán L, Ruffino L, Shen J, et al. Constitutive expression of ErbB-2 in gallbladder epithelium results in development of adenocarcinoma. Cancer Res 2001;61:6971-6
11. Kiguchi K, Ruffino L, Kawamoto T, Ajiki T, Digiovanni J. Chemopreventive and therapeutic efficacy of orally active tyrosine kinase inhibitors in a transgenic mouse model of gallbladder carcinoma. Clin Cancer Res 2005;11:5572-80
12. Pignochino Y, Sarotto I, Peraldo-Neia C, Penachioni J Y, Cavalloni G, Migliardie G, t al. Targeting EGFR/HER2 pathways enhances the antiproliferative effect of gemcitabine in biliary tract and gallbladder carcinomas. BMC Cancer 2010;10:631.
13. Javle M, Churi C, Kang HC, Shroff R, Janku F Surapanenie R, t al. HER2/neu-directed therapy for biliary tract cancer. J Hematol Oncol 2015;8:58 .
14. Trastuzumab in Treating Patients With Locally Advanced or Metastatic Gallbladder Cancer or Bile Duct Cancer That Cannot Be Removed by Surgery, clinicaltrials.gov (Accessed 28 May 2014 at (https://clinicaltrials.gov/ct2/show/results/NCT0047814.)