REVIEW ARTICLE

Human epidermal growth factor (Her-2) in gastric and colorectal adenocarcinoma

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Abstract

Gastrointestinal (GIT) malignancies are a substantial health concern. Most patients present to the clinics with advanced and un-resectable diseases, so it remains difficult to cure with the existing chemotherapeutic regimes. It is therefore extremely important to devise novel therapeutic targets in these neoplasms in order to improve patient's survival. One such target is human epidermal growth factor, also known as Her-2. Although Her-2 expression and the use of α-Her-2 medications in breast cancers is well established, but its expression and potential use as a therapeutic target in gastrointestinal malignancies remains controversial and heavily debated. This review was planned to summarise the available literature extracted from the United States National Library of Medicine (NLM) and Pubmed Central, related to expression of Her-2 in gastric and colorectal adenocarcinomas and their correlation with different parameters. Moreover, we also planned to discuss available data in support of using α-Her-2 in gastric and colorectal malignancies.

Keywords: Her-2, Gastrointestinal neoplasms, Adenocarcinoma.

Introduction

Gastrointestinal malignancies are amongst major oncological problems. Worldwide, stomach cancer is the 5th and colorectal cancer is the 3rd most common cancer.[1] Although the mortality rate of colorectal cancer is controllably low, but gastric cancer ranks as the 3rd leading cause of death worldwide.[1] In Pakistan, an alarmingly rising incidence of both gastric and colorectal carcinomas is being consistently observed in the recent past.[2,3]

Diagnosis of gastrointestinal malignancies is usually made at advanced stages due to non-specific early symptoms of the disease. As a result, the pathology usually remains un-resectable at the time of diagnosis. In terms of therapeutics of gastrointestinal malignancies, chemotherapy remains the main treatment option, but the risk of recurrence remains high. In today's era of personalised medicine, targeted therapy for cancer cells as an adjuvant to chemotherapeutic agents has enhanced the overall survival of cancer patients. One such molecular target which is already being practised in clinics is the human epidermal growth factor receptor (Her-2), which is primarily associated with breast cancer. It is expressed in about 30% of breast cancer cases and is related with worse outcomes compared to Her-2 negative breast cancers. Use of trastuzumab, a monoclonal antibody against Her-2, has shown a dramatic prognosis in breast cancer patients expressing Her-2. With better understanding of Her-2 as a molecular basis for targeted therapy, it has been recognised that this marker is over-expressed in various other cancers, including stomach, colon, ovary, oesophagus, lung, bladder, head and neck.[4]

Expression of Her-2 in gastrointestinal malignancies has been a matter of debate and several groups are exploring these malignancies in order to know if Her-2 is a potential target in gastrointestinal malignancies or not. The current review was planned to discuss available literature to date related to expression of Her-2 in gastric and colorectal adenocarcinomas. Also, it discusses the biology of Her-2 and expression of Her-2 in gastric cancers as well as colorectal cancers. The data in the literature was selected and extracted from publicly available data from the US National Library of Medicine (NLM), National Institute of Health and Pubmed Central. The review, therefore, was not only expected to provide a detailed analysis of available literature, but also to provide propitious platform for future pre-clinical as well as clinical therapeutic trials.

Her-2 Biology and Intracellular Signalling

The protein Her-2 is also known as Neu, CD-340 or p-185 and is encoded by the proto-oncogene ErbB2. Her-2 is a member of "Her" family of proteins and with its normal expression it promotes cellular proliferation and growth. The "Her" family of proteins consists of four structurally related receptor proteins known as Her-1, Her-2, Her-3 and Her-4. When a ligand (usually a growth factor) binds with one of these receptors, they dimerise with each other (in different combinations) resulting in phosphorylation of intracellular sub-units of these receptors. This leads to activation of

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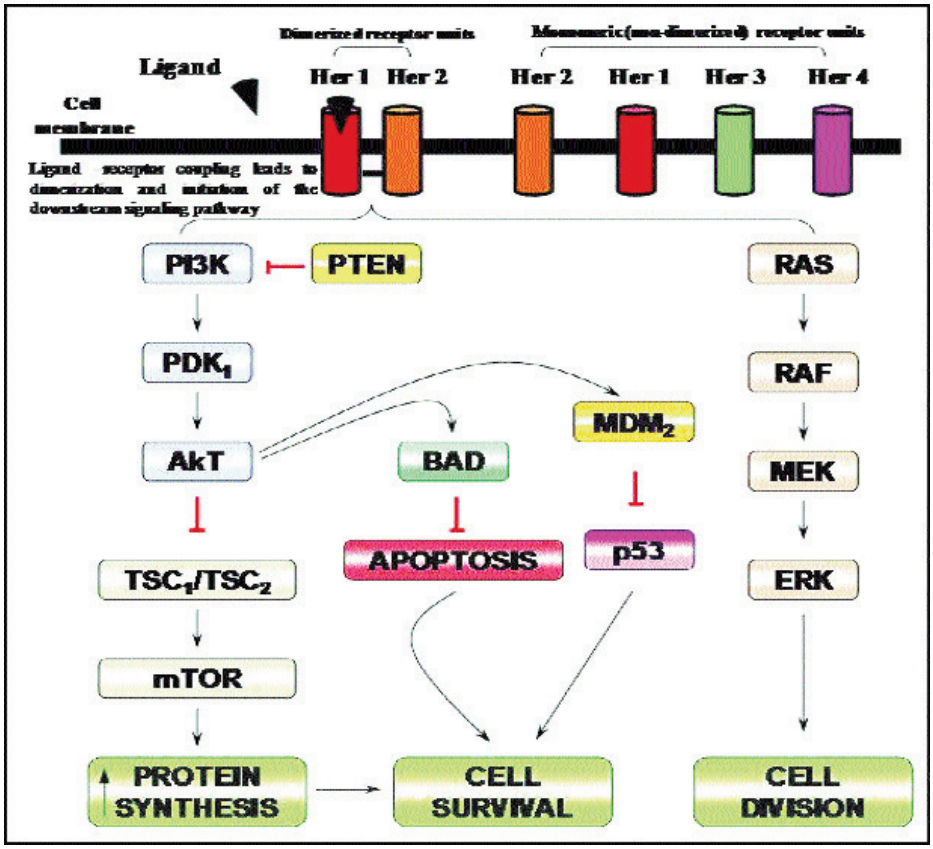

Her: Human epidermal growth factor. PI3K/AKT: Phosphoinositide 3-kinase. PDK1: Pyruvate dehydrogenase kinase. TSC: Tuberous sclerosis. mTOR: Mammalian target of rapamycin. PTEN: Phosphatase and tensin homolog. BAD: Bcl2 associated death promoter protein. MDM2: Mouse double minute 2 homolog. p53: Tumour suppressor gene. RAS: Rat sarcoma. RAF: Rapidly accelerated fibrosarcoma. MEK: Mitogen activated protein kinase. ERK: Extracellular signal regulated kinases.

Figure: Her family of proteins consists of four structurally related receptors Her-1, Her-2, Her-3 and Her-4. When a ligand (usually a growth factor) binds with these receptors, they dimerisewith each other resulting in phosphorylation of intracellular portion of these receptors and activate different pathways. PIK3/AKT a pro-survival pathway, BAD, an antiapoptotic protein, and MAPK through RAF, RAS, and MAP2K/MEK and andERK leads to survival and andproliferation of cells.[5]

various intra-cellular protein pathways, including the Phosphotidyl Inositol 3 (PIK3/AKT) — a prosurvival pathway — Bcl-2-associated death promoter protein (BAD) — an antiapoptotic protein — Mitogenic Activated Protein Kinase (MAPK) through rapidly accelerated fibrosarcoma (RAF) pathway, rat sarcoma (RAS), MAP2K/MEK and extracellular signal regulated kinases (ERK) — survival and proliferation pathway, amongst others[5] (Figure). Over-expression of Her-2 has been most notably associated with increased cellular survival, increased proliferation and decreased apoptotic potential of cells leading to malignant transformation and maintenance of malignancy.

Expression of Her-2 in Gastric Adenocarcinomas

Expression of Her-2 in gastric adenocarcinoma was first described in 1986.[6] Since then it has been a matter of intense debate if Her-2, like breast cancer, can be exploited as a potential prognostic and/or therapeutic target. Various research groups have investigated the expression patterns of Her-2 in gastric adenocarcinoma using various molecular and cellular biology techniques including immunohistochemistry (IHC) as well as fluorescent in situhybridisation (FISH) — with both techniques being concordant at a rate of 95%.[7] Interestingly, Her-2 expression in gastric adenocarcinomas show great variability, 6-35%,[8] establishing a non-consistent pattern. These variable data could be attributed to several factors, including use of different antibodies, different sample size, and use of non-uniform scoring system for interpretation of results amongst others.[9]

Over-expression of Her-2 has been predominantly reported in the intestinal type of gastric adenocarcinoma compared to the diffuse type[8-12] (Table-1). Moreover, correlation of Her-2 over-expression with various factors, including age, gender, tumour grade, tumour stage and prognosis, has been extensively studied. Most of the published data showed that expression patterns of Her-2 do not correlate with patients' age and gender.[13,14] In terms of tumour grade, there is panoply of data to prove that a significant correlation of Her-2 expression exists with well-differentiated[7,15] as well as moderate and poorly-differentiated gastric adenomcarcinomas[16-18] while few noted no association with grade of the tumour[11] (Table-2). Moreover, most of the studies reported a significant association of Her-2 positive gastric adenocarcinomas with advanced stages (stage III/IV)[14,16,17] while few stated with early stages (stage I/II)[15,19] of the tumour and some stated no relation at all with the stage of the cancer.[11,20] In terms of prognosis, it is well established that over-expression of Her-2 is associated with poor prognosis in

Table-1: Her-2 expression in various subtypes of gastric adenocarcinomas.

Reference	Year	No. of cases (n)	Intestinal (%)	Diffuse (%)	Mixed (%)
[11]Tewari M et al	2013	70	45	NS	NS
[8]Mrklic I et al	2012	73	22.5	3.7	0
[10]Dang HZ et al	2012	86	46.9	25.7	0
[14]Wang YY et al	2011	436	51	49	0
[12]Yan B et al	2010	128	59	23	18

Her: Human epidermal growth factor
NS= not stated in the manuscript.

Table-2: Correlation of Her-2+ gastric adenocarcinomas with grade and stage of the tumour.

Reference	Year	Samples (n)	Her-2+ (%)	Association	
				With grade	With stage
[11]Tewariet al	2013	70	21.4	NR	NR
[17]Ieni A et al	2013	304	17.43	III	III/IV
[7]Shan L et al	2013	929	7	I/II	NS
[15]Fan X et al	2013	957	21.73	I	I
[18]Sekran A et al	2012	52	44.2	III	NS
[16]Guiffre et al	2012	109	21.1	III	III/IV
[19]Terashima et al	2011	829	9	I/II	I/II

Her: Human epidermal growth factor
NR: Not related
NS: Not stated in the manuscript

patients with gastric adenocarcinomas,[10,16,17,21] while some data is also available to report no association of Her-2 expression with prognosis.[9,19]

Pakistan is an aetiopathologically distinct region as the risk/genetic factors for developing gastric adenocarcinomas are different compared to the western world. Nevertheless, data regarding Her-2 expression in gastric adenocarcinomas from Pakistan are scanty. A study from Karachi reported that a total of 12% of the investigated gastric adenocarcinoma showed expression of Her-2.[22] Another study from Lahore reported that 66% of the investigated gastrointestinal malignancies (including stomach, small intestine and large intestine) were positive for the expression of Her-2. Of these 66% Her-2+ cases, 30% were gastric adenocarcinoma, 69.6% were large intestine cancer and none of the case was from small intestine. All the positive cases showed a significant association with grades of respective tumours.[23]

It is important to note that there is a great deal of variability when Her-2 expression is investigated amongst several available publications. As described previously, it could be because of several reasons most obvious factor being the technique used in the study. Hofmanne al.studied 168 cases (stomach adenocarcinoma = 149, gastroesophageal junction adenocarcinoma = 16 and oesophageal adenocarcinoma = 3) for Her-2 staining by IHC and FISH, and used Hercep test scoring of breast cancer. The result showed discrepancies between IHC and FISH. They also noted that gastric cancer showed more incomplete baso-lateral membrane staining compared to breast cancer which may be due to high frequency of glandular formation in gastric tissue. To reduce the intra-observer variability and to achieve maximum accuracy, Hofmann et al and Roschoff et al applied scoring criteria for Her-2 in gastric adenocarcinoma which included complete as well as baso-lateral membrane staining of the cell and selection of percentage of cells with 10% cut-off for resection specimens and 5% cut off for biopsy specimens. There was 0/negative for no staining in <10% / <5% of cells; 1+/-ve for faint/barely perceptible baso-lateral membrane staining >10% / >5% of cells; 2+/equivocal for weak to moderate complete membrane or baso-lateral membranous staining in >10% / >5% of cells; 3+/positive for strong complete membrane or baso-lateral membranous staining in >10% / >5% of cells.[4] College of American Pathologists (CAP) and Food and Drug Administration (FDA) have assimilated this proposed scoring.[24] With such objective scoring criteria in place, one can hope for more consistent results.

Expression of Her-2 in Colorectal Adenocarcinomas

There exists contrasting data regarding the over-expression of Her-2 in colorectal adenocarcinoma with a variability of 0-83%.[25] As was true for gastric carcinoma, the variability of Her-2 expression in colorectal carcinoma can also be attributed to several factors, including differences in technical procedures such as tissue storage, incubation time, range of antibodies used and no standard/uniform detection system.[26] In colorectal adenocarcinomas, Her-2 overexpression is membranous as well as cytoplasmic in colorectal cancer cells. Some of the studies followed the breast carcinoma Her-2 scoring protocol by detecting only membranous over-expression which varied between 0-15%, by an average of 5%.[26] As an exception, two studies depicted 41% and 47.4% of cases with membranous Her-2 overexpression out of 170 cases and 137 cases of colorectal carcinomas respectively.[27,28] Some researchers split their scoring in membranous and cytoplasmic over-expression, showing variability between 0-66%,with an average of 30%.[26] Whereas few studies interpreted the results by combining membranous as well as cytoplasmic expression with a variability of 22-83% and an average of 50%[26] (Table-3). A study conducted in Pakistan reported that out of the 100 investigated colorectal cancer samples, 42% showed membranous over-expression of Her-2 in colorectal carcinomas. Moreover, the study also concluded that over-expression of Her-2 was correlated with low (38.7%) and moderate (51.6%) tumour grades compared to the higher grades (9.7%). The same study reported no correlation of Her-2 expression with age, gender and site of the tumour.[29]

A study conducted in India on 40 cases of colorectal carcinomas reported that 65% of the cases showed over-expression of Her-2, with most of them expressing cytoplasmic pattern, three of the cases with cytoplasmic-membranous pattern and none of them were pure membranous. Higher expression of Her-2 was observed in mucinous type (71.4%) compared to the non-mucinous (64.5%).[30] According to this study, there was a significant association of Her-2 positivity in colorectal cancer with increasing age of the patient whereas no relation was found with gender and site of the tumour. It also stated a significant correlation with high grade and high stage of the tumour.[30]

Converse to the aforementioned studies, some of the authors summarised similar findings documenting no correlation between Her-2 expression in colorectal cancer with age, gender, site, grade and stage of the tumour.[28,31] The prognostic significance of Her-2 in colorectal cancer is still controversial. Among some of the publications which analysed prognostic significance of Her-2 in colorectal cancers, several stated worst survival of patients,[26,32] various studies described no correlation[33] while a few studies showed association with well-differentiated tumours.[34]

In summary, the Her-2 expression patterns and their correlation with age, gender, tumour type, grade and stage remain a controversial issue to date. It is therefore important to conduct more studies in order to delineate a clear picture in this regard.

α-Her-2 Medications in Targeted Therapy of Gastric and Colorectal Adenocarcinomas

Trastuzumab is a humanised monoclonal antibody which has affinity for Her-2 receptors and down-regulates the PI3K pathway.[35] It has shown promising results as a targeted therapy in Her-2 positive breast carcinomas. In order to investigate if Trastuzumab can also be used in Her-2+ gastric adenocarcnomas, a randomised controlled phase 3 trial, the ToGA trial (Trastuzumab with

Table-3: Correlation of Her-2+ colorectal carcinomas with grade and stage of the tumour.

Author	Year	Samples (n)	Her-2 +ve (%)			Grade	Stage
			M	C	M+C		
[31]Seo AN et al	2014	365	6	-	-	NA	NA
[30]Gill MK et al	2011	40	-	57.5	7.5	II/III	III/IV
[29]Anwar S et al	2010	100	42	-	-	I/II	NS
[34]Kruszweskiet al	2010	202	26.7	66.3	-	NA	NA
[32]Tavangar SM et al	2005	55	-	-	21.8	II/III	III

Her: Human epidermal growth factor
M: Membranous
C: Cytoplasmic
M+C: Membranous+cytoplasmic expression
NA: Not associated
NS: Not stated in the manuscript.

chemotherapy in Her-2-positive gastric cancer) was conducted at 122 centres in 24 countries involving 3803 gastric and gastroesophageal junctional adenocarcinoma patients. Of these patients, 810 (22%) were Her-2-positive. The Her-2+ patients were divided into 2 groups: patients in group I were treated with chemotherapy and trastuzumab, and patients in group II were treated with only chemotherapy. The patient survival for group I was 13.8 months while that for group II was 11.1 months. This corresponded to 26% reduction in death rate of patients treated with trastuzumab and 36% reduction in death rate of patients treated with trastuzumab who expressed high Her-2 receptor. Based on the results obtained from the ToGA trial, trastuzumab has been approved in Japan, USA and Europe for those gastric adenocarcinomas which show over-expression of Her-2 at a score of +3 in IHC and a positive score at FISH+.[36] Favourable outcomes of trastuzumab with chemotherapy has been stated by few of the case reports.[37,38] More clinical trials are underway to develop and introduce other anti Her-2 drugs in clinical practice for Her-2 positive gastric cancer patients.[24,39]

Use of α-Her-2 therapy in the treatment of colorectal cancer patients has been less extensively investigated compared to gastric adenocarcinomas. National Cancer Institute conducted a phase II trial amongst colorectal cancer patients exhibiting a low level of Her-2 expression (8%). However, when these patients were treated with herceptin and irinotecan, they all responded to the therapy.[40] As studies mentioned cytoplasmic expression of Her-2 in colorectal cancer cells, an intracellular kinase inhibitor, Lapatanib, has been recently approved for Her-2-positive breast carcinoma which is under trial for the treatment of cytoplasmic Her-2-positive colorectal carcinomas.[26]

In summary, increasing focus is being out on using α-Her-2 therapy for the treatment of gastric and colorectal adenocarcinomas, opening a new era of personalised medicine in the therapeutic and prognostic fields of gastrointestinal malignancies.

Conclusion

The review discussed the available data regarding the expression of Her-2 in gastric and colorectal cancer. Although with the support of encouraging ToGA trial, target therapy has been approved for advanced gastric cancer, but Her-2 testing has not gained popularity in most parts of the world and more so is true for the α-Her-2 therapy. We recommend a scheduled guideline for Her-2 testing in all cases of gastric cancer which could help in treatment and in terms of patient survival. Role of Her-2 in colorectal cancer is even more debatable. More multicentre studies, probably with unified parameters, are required using larger sample size to illuminate these issues.

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