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Review Article

HER2: An emerging biomarker in non-breast and non-gastric cancers

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ABSTRACT

Introduction: HER2, a member of the human epidermal growth factor (HER) family of transmembrane tyrosine kinases, has been of considerable interest in oncology due to its significant role in the pathogenesis of various cancer types.
Materials and methods: In this article, we review current data on HER2 as a potential biomarker in cancers other than breast and gastric by conducting an electronic database search using Pubmed.
Results: The existing literature provides evidence that HER2 protein overexpression and genomic alterations exist in a subset of patients with non-breast and non-gastric cancers, and hints at the promise of anti-HER2 targeted therapy in these patients.
Conclusion: Moving forward, the rigorous evaluation of HER2 (protein and genomic) status as a predictive biomarker will be necessary to bring anti-HER2 therapeutics for non-breast and non-gastric cancers to the clinic.
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1. Introduction

HER2 (human epidermal growth factor 2) is a membrane-bound tyrosine kinase in the ERBB family. The HER2 monomeric protein has three main regions: the extracellular amino-terminal region comprising four domains (I–IV), the hydrophobic transmembrane domain and the carboxy-terminal kinase domain comprising the juxtamembrane domain, tyrosine kinase and C-terminal tail with autophosphorylation sites. It has no known ligand, and heterodimerizes with other members of ERBB family on ligand binding to stimulate various intracellular signal transduction pathways involved in cell growth [1,2].

HER2 protein overexpression, gene amplification and mutation have been identified in a variety of cancer types. Evaluation of HER2 status is now critical as a companion diagnostic for anti-HER2 targeted therapeutics. There are two different strategies for targeting HER2 that have been successfully employed in the clinic: 1. antibodies directed against the extracellular domain of the receptor and 2. small molecule Tyrosine Kinase Inhibitors (TKIs) acting on the intracellular kinase domain. Several agents targeting HER2-positive malignancies have been approved, including trastuzumab and pertuzumab (humanized monoclonal antibodies); lapatinib and afatinib (dual EGFR/HER2 inhibitors); and ado-trastuzumab emtansine (T-DMI) (an antibody-cytotoxic conjugate that combines the HER2-targeting anti-tumour property of trastuzumab with the cytotoxic microtubule-depolymerizing compound DM1) [3,4].

A brief description of trastuzumab is provided because of its distinction as the first anti-HER2 targeted therapeutic to enter the clinic. Trastuzumab exerts its anti-tumour effects via different mechanisms, one of them being the inhibition of intracellular signal transduction. In *HER2*-amplified human breast cancer cells, trastuzumab inhibits HER2 activation/phosphorylation, with subsequent effects on downstream signalling pathways such as the PI3K-Akt-mTOR and Ras-Raf-Mek-Erk1/2 pathways which are known to be tumorigenic [5]. Trastuzumab also promotes antibody-dependent cell-mediated cytotoxicity (ADCC). Evidence from in vitro and in vivo studies indicate that trastuzumab efficiently induces ADCC against HER2-positive breast cancer cells [6–9]. Trastuzumab also triggers apoptosis [10], blocks the formation of phosphorylated p95 (a constitutively active membrane-bound HER2 protein fragment) [11], and inhibits tumour angiogenesis [12]. The score of Her2 protein for clinical purposes is well established in the case of breast cancer [13–15].

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The presence of HER2 alterations in diverse cancers provides novel therapeutic opportunities. In this review, we survey and describe the prevalence of HER2 alterations in non-breast and non-gastric cancers. As a corollary, we also highlight the need for molecular pathologists to recognize the importance of accurate and reproducible HER2 testing.

2. Strategy of review

An electronic database search using Pubmed was conducted. The following keywords and terms were used in the search: HER2 in cancer; lung cancer; salivary gland tumour; ovarian cancer; endometrial cancer; uterine cervix cancer; prostate cancer; bladder cancer; oesophagus cancer; colorectal cancer; biliary tract cancer; pancreatic cancer; liver cancer; head and neckcancer; astrocytoma; glioblastoma; hepatocellular carcinoma; melanoma; germ cell tumour. Clinical studies, meta-analyses and systematic review analysing HER2 in cancers other than breast and gastric were all included. Only articles in the English language were selected.

A total of 251 papers were screened and analysed; from these, 163 were included.

3. Results

3.1. HER2 in lung cancers

To date, there have been several studies concerning *HER2* mutations in non-small cell lung cancer (NSCLC). *HER2* mutations have been reported to exist in up to 5% of non-small cell lung cancer (Table 1). Similar to EGFR-driven NSCLC, *HER2* mutations are more commonly seen in NSCLC patients with the following characteristics: Asian, female gender, light/never-smoker status and adenocarcinoma histology [18–22]. Most *HER2* hotspot somatic mutations are located in exon 20. The mutations are located in the C-helix region of the kinase domain, similar to those found in *EGFR*. A study by Sasaki et al. in a Japanese population [19], and Arcila et al [23] in a large cohort of predominantly Caucasian patients, revealed a 12 nucleotide insertion (YVMA) in exon 20 at codon 775. Another study reported seven of nine cases with in-frame duplication or insertions at codon 776–779 (YVMA) and two showed base substitutions resulting in amino acid changes [24]. Mazieres et al. found HER2 to be anear-exclusive driver in approximately 2% (65/3800) of NSCLC, save for one case with a concomitant *KRAS* mutation [25].

HER2 protein overexpression and gene amplification have been described in 7%–23% [26–28] and 2%–22% [26,29,30], respectively, of NSCLC patients. In a meta-analysis of 2579 NSCLC patients, HER2 IHC overexpression was associated with a poor prognosis in adenocarcinoma [31]. Another meta-analysis of 6135 patients by Liu et al. also identified HER2 protein overexpression as a poor prognostic marker in lung cancer [32].

A few early clinical trials exploring the outcomes of treatment with trastuzumab either as monotherapy or combined therapy have shown only modest or minimal clinical benefit in HER2 IHC-positive NSCLC [33,34]. However, a trend towards better clinical outcome was seen in patients treated with trastuzumab combination therapy in HER2 3+ positive overexpression or FISH-positive NSCLC [35,36]. Ross et al. reported a case of *HER2*-amplified NSCLC showing a 51% regression in tumour size after lapatinib monotherapy [37].

Patients with advanced NSCLC harbouring *HER2* mutations have reportedly displayed evidence of response when treated with combined anti-HER2 agents [25,38–41]. For example, Mazieres et al. observed a durable response in a study of 22 patients receiving anti-HER2 treatment, with 11 patients achieving partial responses and 4 patients with disease stabilization [25]. Similarly, treatment with afatinib, an EGFR/HER2 inhibitor, resulted in objective responses in 3 NSCLC patients with *HER2* kinase domain mutations.

3.2. HER2 in salivary gland tumours

Malignant tumours of salivary gland are rare lesions and often have poor prognoses [42]. The prevalence of HER2 protein overexpression in salivary gland tumours ranges from 4 to 21% [43–46]. Salivary gland carcinoma comprises a wide spectrum of histological subtypes, and among these, the subtype reportedly with the highest prevalence of HER2 protein overexpression/amplification is salivary duct carcinoma (SDC) [47–53] (Table 2). The jury is still out concerning the prognostic role of HER2 expression in salivary gland tumours [48,53,59].

SDC represents 1–3% of all malignant salivary glands tumours and resembles high-grade ductal carcinoma of the breast histologically. It is an aggressive tumour with a high risk of local and distant recurrence, and is associated with high mortality and poor response to treatment. It can arise de novo or as the malignant component of carcinoma ex-pleomorphic adenoma. In view of the poor outcomes, several therapeutic approaches have been studied. Several studies reported encouraging results for trastuzumab-based chemotherapy in HER2-positive SDC [54–61].

Table 1
Frequency of *HER2* mutations in lung cancer.

Group	Total number (n)	Frequency (%)
Stephens P et al. (Nature 2004)	120	4
Shigematsu HI et al (Cancer Research 2005)	671	1.6
Buttitta FI et al. (International Journal Cancer 2006)	403	2.2
Sasaki H et al. (2006)	122	0.8
Sun Y et al. (2010)	52	3.8
Tomizawa K et al (2011)	504	2.6
Li C et al. (2012)	224	3.6
Cardarella S et al (2012)	344	4.3
Zhang Y et al (2012)	266	4.6
Arcila Mat et al (2012)	1478	1.7
Mazieres JI et al (2013)	3800	1.7
Kris MG et al. (JAMA 2014)	733	2.6

Table 2
Frequency of HER2 protein overexpression and amplification in salivary duct carcinoma.

Group	Total number	Protein overexpression	Amplification
Cornolti G et al. (Arch Octolaryngol Head Neck Surg 2007)	13	10/13	8/10
Jaehne M et al. (Cancer 2005)	34	7/34	1/7
Clauditz TS et al (Pathology 2011)	14	3/14	3/3
Nardi V et al (Clin Cancer Res 2013)	27	–	8/27
Skalova A et al. (Pathol Res Pract 2001)	15	14/15	–
Skalova A et al. (Histopathology 2003)	11	11/11	4/11
Etges A et al. (J Clin Pathol 2003)	5	4/5	–
William MD et al. (Clin Cancer Res 2010)	66	10/66	6/10

3.3. *HER2 in ovarian cancer*

HER2 protein overexpression occurs in 5–19% of epithelial ovarian cancer (EOC) (Table 3) [62–70].

Among the various histological subtypes of epithelial ovarian carcinomas, it appears that HER2 gene amplification and protein overexpression is most common in the mucinous subtype. Table 4 provides a breakdown of HER2 status by histological subtype.

Somatic *HER2* mutations have also been identified in epithelial ovarian carcinomas. Lin et al. [76] reported the presence of *HER2* mutations in 2 *HER2*-amplified ovarian mucinous carcinoma cases. An insertional mutation (amino acids 772–775, YVMA) was identified in exon 20 of *HER2* in another study [77].

At present, the prognostic utility of HER2 overexpression in ovarian cancers is unascertained [78,79].

The results of an early clinical trial for anti-HER2 targeted therapy in epithelial ovarian carcinomas were disappointing [63]. In this study, there was no documentation of *HER2* genomic amplification status, and the study cohort did not include any mucinous carcinomas. More recent studies provide circumstantial evidence that mucinous carcinomas might respond to anti-HER2 therapeutics [80,81].

3.4. *HER2 in pancreatic cancer*

Pancreatic cancer is an aggressive tumour; 5-year survival rates are generally less than 5% [82], and treatment options are limited [83].

The prevalence of HER2 overexpression in pancreatic cancer ranges from 7% to 61% and 2%–24% respectively (Table 5) [84–88].

The role of HER2 status as a prognostic marker in pancreatic cancer is at present equivocal. Sharif et al. and Stoecklein et al. found no association of *HER2* amplification with patient outcome [86,87]. This is in contrast to Komoto et al. [85]who reported significantly shorter survival times in patients with HER2 overexpression.

With regards to anti-HER2 the rapeutics for pancreatic cancer, the data to date has not been encouraging. A phase II study by Harder et al. [84] did not demonstrate improved survival in HER2-positive pancreatic carcinomas treated with trastuzumab and capecitabine compared with standard chemotherapy. Safran et al. reported no significant improvement of survival in patients treated with trastuzumab and gemcitabine in HER2-positive pancreatic carcinoma [89].

Table 3
HER2 protein overexpression and amplification in epithelial ovarian carcinoma.

Group	Total number	Protein overexpression %	Amplification %
Hogdall EV et al. (Cancer 2003)	181	13.3%	–
Bookman MA et al. (J Clin Oncol 2003)	837	11.4%	–
Camilleri-Broet et al. (Ann Oncol 2004)	95	15.8%	–
Lee CH et al. (Int J Gynecol Pathol 2005)	102	4.9%	2%
Mano MS et al. (Gynecol Oncol 2004)	64	–	12.5%
Tuefferd M et al. (PLoS One 2007)	320	12.8%	6.6%
Steffensen KD et al. (Int J Oncol 2008)	99	14.1%	–
Vermeij J et al. (BMC 2008)	31	19.4%	9.7%
Farley J et al. (Gynecol Oncol 2009)	133	–	6.8%

Table 4
HER2 amplification in epithelial ovarian carcinoma based on histological subtypes.

Histological types	Amplification (%)	References
Serous papillary	3%	[71]
	7%	[74]
Endometrioid	2.1%	[71]
Mucinous	25%	[71]
	35.3%	[72]
	18.8%	[75]
Clear cell	4%	[71]
	14%	[73]
Mixed type	11.9%	[71]

Table 5
HER2 protein overexpression and amplification in pancreatic cancer.

Group	Total number	Protein overexpression (%)	Amplification (%)
Harder J et al. (Br J Cancer 2012)	207	26%	3.9%
Komoto M et al. (Cancer Sci 2009)	129	61.2%	–
Stoecklein NH et al. (J Clin Oncol 2004)	50	10%	24%
Sharif S et al. (Dig Dis Sci 2008)	63	25.4%	–
Chou A et al. (Genome Med 2013)	469	7.2%	2.1%

3.5. *HER2 in endometrial cancer [90–111]*

Endometrial carcinoma is the most common gynaecological malignancy [90], and histological subtypes include endometrioid, serous and clear cell carcinomas [91].

The prevalence of HER2 overexpression and amplification in endometrial carcinomas ranges from 17% to 52% and 11%–21% respectively [92–95], and appears to be most frequent in the serous histological subtype [96–98]. Table 6 provides a breakdown of HER2 overexpression/amplification status by histological subtype. Similar to breast and gastric carcinomas, intratumoral genetic heterogeneity has been documented in endometrial serous carcinomas [109] (see Table 7).

Several studies have evaluated the response of HER2-positive endometrial carcinomas to anti-HER2 therapeutics. Clinical responses to trastuzumab have been documented in HER2-overexpressing endometrial carcinomas [110,111].

3.6. *HER2 in colorectal cancer*

Unlike breast and gastric cancers, the prevalence of HER2 membranous overexpression in colorectal cancers appears to be low (1%–6%) [112–117]. However, if cytoplasmic overexpression is included, the prevalence appears to be higher (26%–48%) [118–120]. The clinical significance of cytoplasmic expression is at present unknown.

Somatic *HER2* kinase domain mutations have also been reported in 3 out of 104 patients (2.9%) [121].

Partial responses to anti-HER2 therapeutics, in combination with other agents, have been reported in colorectal cancer patients [122]. The combination of cetuximab and pertuzumab in refractory colorectal cancer was associated with some anti-tumour activity despite intolerable drug toxicities [123].

Table 6
HER2 protein overexpression and amplification in endometrial cancer (based on histology and grade).

Group	Tumour subtype	Protein overexpression (%)	Amplification (%)
Morrison C et al. (J Clin Oncol 2006)	Endometrioid		
	- Grade 1	3%	1%
	- Grade 2	7%	3%
	- Grade 3	29%	8%
	Mixed epithelial	26%	7%
	Malignant	12%	4%
	Muellerian tumour		
	Serous	43%	29%
	Clear cell	33%	22%
Grushko TA et al. (Gynecol Oncol 2008)	Serous	60.5%	21.4%
	Non-serous	41.3%	10.6%
	Non-serous:		
	- Grade 1	3.1%	–
	- Grade 2	3.9%	–
	- Grade 3	21.2%	–
Konecny GE et al. (Br Cancer 2009)	Serous	–	17%
	Clear cell	–	16%
	Endometrioid	–	1.4%
Xu M et al. (Histopathology 2010)	Serous carcinoma	10.7%	12%
	Endometrioid	1%	0

Table 7
HER2 overexpression and amplification in Uterine Serous Carcinoma.

Group	Total number	Protein overexpression (%)	Amplification (%)
Santin AD et al. (Clin Cancer Res 2002)	10	80%	–
Slomovitz BM et al. (J Clin Oncol 2004)	68	18%	2.9%
Santin AD et al. (Am J Obstet Gynecol 2005)	30	–	47%
Diaz-Montes TP et al. (Gynecol Oncol 2006)	25	48%	–
Villella JA et al. (Int J Gynecol Cancer 2006)	19	–	–
Odicino FE et al. (Int J Gynecol Cancer 2008)	12	16.6%	16.6%
Togami S et al. (Cancer Sci 2012)	71	14%	–
Santin AD et al. (Gynecol Oncol 2005)	26	62%	42%

Table 8
HER2 overexpression and amplification in oesophageal cancer.

Group	Total number (n)	Protein overexpression	Amplification	Protein overexpression and or amplification (%)
Chan DS et al. (J Gastrointest Surg 2012)[a]	1464	–	–	21.9%
Slotta-Huspenina J et al. (Cancer (Basel) 2014[a])	127	–	–	30.7%
Langer R et al. (Mod Pathol 2011)[a]	142	–	–	28.9%
Rossi E et al. (Histopathology 2010)[a]	13	–	–	38.5%
Yoon HH et al. (Clin Cancer Res 2012)[a]	713	–	–	17%
Reichelt U et al. (Mod Pathol 2007)[a]	110	–	–	14.5%
Thompson SK et al. (Ann Surg Oncol 2011)	89	–	–	15.7%
Hu Y et al. (Mod Pathol 2011)	116	–	–	18.1%
Zhan N et al. (Med Oncol 2012)[b]	145	41.4%	4%	–
Mimura K et al. (Br J Cancer 2005)[b]	66	13.6%	10.6%	–
Gonzaga IM et al. (BMC 2012)[b]	69	18%	16.6%	–

[a] Adenocarcinoma cases.
[b] Squamous cell carcinoma.

3.7. *HER2 in oesophageal cancer*

The prevalence of HER2 overexpression and/or genomic amplification in oesophageal cancers ranges from 15% to 39% (Table 8) [124–134].

Although there is a paucity of data concerning the efficacy of anti-HER2 therapeutics in oesophageal cancers, it is noteworthy that complete response to lapatinib was documented in a single case of *HER2*-amplified oesophageal adenocarcinoma [135].

3.8. *HER2 in other cancers*

In addition to the cancers discussed above, HER2 overexpression, amplification and mutation has been reported in other cancer types. In bladder cancer, amplification and/or overexpression were also identified. However, the exact figures for HER2 overexpression and/or amplification incidence are still uncertain, and vary from 9% to 76% for overexpression [136–144] and 5%–42% for genomic amplification [137,139,141,142,145–147]. A large multicentre series investigating 1005 primary invasive bladder carcinomas by Lae et al. found HER2 protein overexpression in 9.2% of tumour samples [139].

For biliary tract cancer, the prevalence of HER2 overexpression ranges from 9% to 20% [148–153]. Harder et al. [150] and Pignochino et al. [152] reported a frequency of 5% and 8% for genomic amplification.

Several published studies have reported HER2 overexpression (3–50% prevalence) in uterine cervical cancer [154–157]. Lesnikova et al [157] reported 5 cases of amplification in 136 patients with invasive cervical cancer. Two other studies of cervical squamous cell carcinomas reported a HER2 overexpression and/or amplification prevalence of approximately 20% [158,159].

For the head and neck squamous cell cancer, the prevalence of HER2 protein expression was reported to be between 2% and 50% [160–162]. Hanken et al. [162] observed a prevalence of 3% *HER2* amplification in a study of 207 patients with oral squamous cell carcinoma (Table 9).

4. Conclusion

As our review highlights, HER2 protein overexpression/genomic amplification appears to be present in many different cancer types, and there are ongoing studies evaluating the utility of anti-HER2 therapeutics in these populations. The considerable variation in the reported rates of HER2 protein overexpression and gene amplification within different individual cancer types suggests that a significant effort in ensuring full laboratory quality assurance (similar to what has been encountered in breast and gastric cancer) will have to be delivered for HER2 testing to become a companion diagnostic in many solid tumours.

Some lessons may be gleaned from the experience with HER2 testing in breast and gastric cancer. Despite the accumulated wisdom concerning HER2 analysis for breast cancer over the last decade [13,14], no absolute 'gold standard' yet exists. The latest American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) HER2 testing algorithm [16], which recommends a second confirmatory method in equivocal cases i.e. immunohistochemistry (IHC) followed by fluorescence in-situ hybridization (FISH), has been noted by some authors to be suboptimal in non-specialized laboratories [17]. Molecular pathologists involved in the development of HER2 testing algorithms for non-breast and non-gastric cancers will thus need to be cognizant of quality assurance issues moving forward.

The repositioning of known drugs in new cancer paradigms is as important for the improvement of cancer care as the generation of new drugs. In that sense, HER2 testing and anti HER2 therapy may represent, yet again, the model for other drugs with accompanying biomarkers to follow.

Table 9
Frequency of *HER2* overexpression, amplification and mutation in other cancers.

Cancer	Protein overexpression	Amplification&/or HER2 positive	References
Urinary bladder	9–76%	5–42%	[136–147]
Biliary tract and gall bladder	4–20%	5–8%	[148–153]
Uterine cervix	3–50%	4–22%	[154–159]
Head and neck/oral SCC[a]	2–50%	3% & 9%	[160–162]

[a] SCC (Squamous cell carcinoma).

Conflict of interest statement

I wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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