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Targeting human epidermal growth factor receptor 2 (HER2) in gynecologic malignancies

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Abstract

Purpose of review—The purpose of this review is to describe the role of the human epidermal growth factor receptor 2 (HER2) as a biomarker and potential target in gynecologic malignancies and to describe contemporary updates in the use of anti-HER2 treatments for these cancers.

Recent findings—Approximately 25–30% of all patients with uterine serous carcinoma overexpress tumoral HER2. The anti-HER2 antibody trastuzumab represents an effective, targeted therapy with significant efficacy in the treatment of HER2-positive breast and gastric cancer. Recently, trastuzumab efficacy has also been demonstrated in a randomized controlled trial of women with advanced or recurrent uterine serous carcinoma. Additionally, trastuzumab may be effective in women with HER2-positive uterine carcinosarcoma. The role of anti-HER2 therapy is unclear in women with other gynecologic malignancies but is being evaluated.

Summary—HER2 amplification/overexpression is an effective therapeutic target in select gynecologic malignancies, and especially in the rare endometrial cancer subtype, uterine serous carcinoma. As anti-HER2-targeted therapies become increasingly available, more treatment options may become available for women with HER2-positive disease.

Keywords

biomarker; human epidermal growth factor receptor 2; ovarian cancer; uterine serous carcinoma

INTRODUCTION

The oncogenic potential of human epidermal growth factor receptor 2 (HER2) is widely recognized. Overexpression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast, gastric, and uterine cancers, [1–4]. Although the protein has become an important biomarker and target of therapy for up to one-third of breast cancer patients, in recent years it has also been

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identified that 25–30% of patients with the rare endometrial subtype, uterine serous carcinoma (USC), also overexpress HER2.

When used together with cytotoxic chemotherapy the addition of trastuzumab, a monoclonal anti-HER2 antibody, improves survival in patients with HER2-positive breast, gastric, and uterine serous carcinoma [1,2–4]. Additionally, the family of anti-HER2 agents has expanded in recent years with the addition of small molecule inhibitors (i.e., lapatinib), antibodies (i.e., pertuzumab), and an antibody–drug conjugate (i.e., ado-trastuzumab emtansine, T-DM1) [5,6]. In this review, we discuss the role of HER2 as an oncogene, the incidence of HER2-positive gynecologic malignancies, and contemporary treatment updates, including how the development of anti-HER therapies for these cancers is revolutionizing outcomes for women with HER2-positive cancers.

FUNCTION OF HER2 IN NORMAL TISSUE AND CANCER

HER2 amplification in human breast cancers was first noted in 1985 [7], and since then a large body of evidence has supported the role of HER2 as a predictive biomarker and therapeutic target in human cancer.

HER2 is a receptor tyrosine kinase that is present on the cell surface. It is a member of the ERBB protein family. Nomenclature for these receptors has evolved and is often used interchangeably. The first protein in the family discovered was named epidermal growth factor receptor (EGFR) and thus the ERBB receptors are commonly known as the EGFR receptor family. The ERBB/EGFR family consists of HER1, HER2, HER3, and HER4 (Table 1). Each receptor consists of three domains: the extracellular region, which binds ligands, the transmembrane spanning region, and the intracellular cytoplasmic tyrosine kinase domain [8].

In normal tissue, these receptors are activated through ligand binding which then causes receptor dimerization. Notably, HER2 does not directly bind a ligand, but instead undergoes heterodimerization with other HER family members or homodimerization with other HER2 receptors. HER2 dimerization then activates various signaling pathways inside the cell, including the PI3K/AKT pathway, the RAS/MAPK pathway, and the JAK–STAT pathway [9]. Functionally, HER2 is expressed in a variety of normal tissues and mediates proliferation, differentiation, and apoptosis [10].

The role of HER2 in cancer has also been well established [11]. In general, growth factor receptors (such as HER1/EGFR and HER2) can lead to prooncogenic states through various mechanisms. Amplification of the ERBB2 gene is the most common way that HER2 is overexpressed in cancer. Gene amplification leads to increased transcription and therefore increased receptor expression which promotes HER2 activity. The ERBB2 gene can also be mutated or rearranged. In the case of gene mutations, the receptor is often constitutively dimerized which leads to ongoing activation of the receptor.

HER2 is overexpressed in a variety of solid tumors including breast, gastric, esophageal, head and neck, and gynecologic cancers [12,13–15]. Cancers that overexpress HER2 are often treated with HER2-directed therapy. Trastuzumab, a monoclonal antibody directed at

HER2, was the first drug approved by the US Food and Drug Administration (FDA) in 1998 for treating HER2-positive metastatic breast cancer. Five additional agents have now been approved by the FDA [15] (Table 2). Pertuzumab is also a monoclonal antibody that targets a different HER2 epitope and it is approved for use in combination with trastuzumab for HER2-positive breast cancer [16]. Lapatinib is an oral small-molecule tyrosine kinase inhibitor that inhibits both HER1 and HER2. It is approved in combination with capecitabine or letrozole for the treatment of HER2-positive breast cancer. Neratinib and afatinib are other oral tyrosine kinase inhibitors that bind EGFR/HER1, HER2, and HER4. Neratinib is approved for the extended adjuvant treatment of HER2-positive early-stage breast cancer [17]. Afatinib's use in breast cancer is limited, but it is FDA approved for the treatment of EGFR-mutated nonsmall cell lung cancer (NSCLC) as well as progressive squamous NSCLC [18]. More recently, ado-trastuzumab emtansine (a form of trastuzumab that incorporates the microtubule inhibitor DM1) was approved for the treatment of HER2-positive breast cancer in patients with residual disease after neoadjuvant therapy that included trastuzumab [19]. This formulation allows for more selective delivery of the drug to HER2-positive cells.

Although there are no FDA approved indications for HER2-targeting agents in gynecologic cancers, translational research and clinical trials are underway which may alter the treatment paradigm of HER2-positive gynecologic cancers.

TESTING FOR HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2

Approved algorithms exist for scoring HER2 expression and amplification in breast and GI carcinomas. Notably, no validated criteria currently exist for gynecologic cancers. Typically, the American Society of Clinical Oncology/College of American Pathologists breast cancer algorithms are employed [12[■],20]. In the most recent 2018 algorithms, tumors are first evaluated for protein expression with an immunohistochemistry (IHC) assay. Results are given based on a percentage of tumor cells that are positive for HER2 as well as the completeness of membrane staining. Results are reported on a scale of 0–3. Cases that are 0 or 1+ are considered negative for HER2 expression. Cases that are 3+ are considered positive. If the scoring is 2+ (defined as incomplete/weak staining in >10% of tumor cells or complete/intense staining in <10% of tumor cells), the tumor is then subject to in-situ hybridization (ISH).

ISH assay testing uses a probe to locate a specific sequence of DNA; therefore, results are reported as an average number of HER2 copy number signals per cell. Based on the average signals per cell, results are reported as positive (>6 signals/cell), negative (<4 signals/cell) and equivocal (between 4 and 6 signals/cell). Equivocal tests in this scenario are subject to repeat testing using a new specimen or dual-probe ISH [20].

It is notable that interpreting HER2 expression via IHC can be prone to subjectivity and correlation between IHC and ISH can be poor (typically IHC overestimates HER2 amplification) [21]. Ultimately, validating HER2 testing in gynecologic cancers requires not only consistency among testing platforms, but also correlations between testing and

outcomes of targeted therapy. Given the relative rarity of HER2-positive gynecologic tumors and limited clinical trial data, validated testing has not yet been achieved.

In the last few years, multiple next-generation sequencing (NGS) platforms for tumor testing have begun to revolutionize cancer treatment. However, limited and controversial data exist that compare ERBB2/HER2 assessment by NGS methods with traditional methods (IHC and ISH). For example, a recent study showed high concordance of HER2 status by NGS and IHC/ISH in breast and gastroesophageal cancer [22]. In contrast, in a study including 60 uterine tumors, the concordance of IHC and/or ISH with NGS was only 43% [23]. Although the reason for this difference in results is poorly understood, intratumoral heterogeneity of HER2 expression and amplification in these type II endometrial carcinomas may potentially explain the low concordance.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 IN UTERINE CANCER

Decades of research have informed the utility of HER2 testing and HER2-targeted therapies in breast cancer; however, the story of HER2 in gynecologic malignancies is only more recently being told. Data are emerging from site specific as well as basket trials that are now informing our understanding of HER2 in gynecologic malignancies.

Uterine serous carcinoma

Uterine serous carcinoma (USC) is an aggressive form of endometrial cancer and is associated with a poor prognosis. It represents only 10% of endometrial cancers but is disproportionately associated with 40% of endometrial cancer-related deaths [24]. Compared with patients with endometrioid endometrial carcinoma (often referred to as type I uterine cancer), patients with USC are often older, more likely to be African-American, and less likely to be obese or have excessive estrogen exposure [2]. Patients are more frequently diagnosed at an advanced stage and have higher risk for recurrence. Current recommendations for the adjuvant treatment of almost all women with USC include platinum and taxane-based chemotherapy [25,26].

USCs often overexpress HER2. The rates of HER2 overexpression or amplification vary tremendously in the literature. Single institution reports have evaluated consecutive series of women with USC and HER2 overexpression has ranged from 18 to 42% of cases and gene amplification range from 16 to 47% [27–30]. In 2008, the Gynecologic Oncology Group (GOG) analyzed a large cohort of women treated on protocol GOG177 with advanced or recurrent endometrial carcinoma. Among the USC tumors, 21% showed HER2 gene amplification and 61% demonstrated strong IHC staining [31].

More recently, The Cancer Genome Atlas Research Network analyzed 373 endometrial cancers, including 66 USCs. HER2 was amplified (with associated protein overexpression) in 27% of the USC cases [32]. In an analysis of tumor collected as part of the GOG210 protocol, 313 USC tumor samples were studied. Surprisingly, less than 5% of these tumors demonstrated HER2 overexpression [33]. The reasons for the discrepancies in HER2

expression and amplification across studies is unclear but may be related to a lack of clear guidelines for performing and interpreting these tests.

Human epidermal growth factor receptor 2 in other uterine cancers

HER2 expression and amplification have been noted in other histologic subtypes of endometrial cancer. Like USC, results vary among studies as well as among various testing platforms. Low-grade endometrioid tumors have universally demonstrated low expression and amplification [29,34], whereas rates of overexpression are higher in grade 3 tumors (12–31%) [35,29]. However, in one series that only performed ISH, 0 of 40 grade 3 tumors demonstrated amplification [34].

Owing to its rarity, less is known about HER2 in clear cell uterine carcinoma. In small series of clear cell carcinoma patients, rates of amplification range from 16 to 24% [34,36]. In a recent study of uterine carcinosarcoma, 13 of 80 patients (16%) were HER2 positive based on IHC or FISH testing [37]. All 13 of the positive cases had either serous or mixed carcinoma component (as opposed to endometrioid, clear cell, or neuroendocrine histotypes) and heterogeneity of protein expression was common [37].

Clinical trials involving human epidermal growth factor receptor 2-targeted therapy in uterine carcinoma

Given this clinically significant rate of HER2 overexpression, treatment with trastuzumab has been studied in women with endometrial carcinoma. Fleming *et al.* [38] evaluated single-agent trastuzumab in women with measurable stage III, IV, or recurrent endometrial cancer. No clinical benefit was noted in this trial. However, the study was criticized because of the fact the majority of tumors was actually type I (endometrioid) tumors and less than half of tumors demonstrated HER2 amplification by ISH.

Lapatinib has also been studied in women with advanced endometrial cancer. Thirty women were enrolled in a Gynecologic Oncology Group phase II trial. Only one partial response was noted and neither HER2 overexpression nor gene amplification was associated with tumor response [39].

More recently, Fader *et al.* evaluated 61 patients with advanced or recurrent uterine serous carcinoma overexpressing HER2 [1]. In this phase II trial, patients were randomized to receive carboplatin and paclitaxel with or without trastuzumab. Patients who received trastuzumab had an improved progression-free survival of 12.6 versus 8.0 months ($P=0.005$) with a hazard ratio (HR) of 0.44 (95% confidence interval [CI] 0.26–0.76) [1]. When examining the subcohorts, median progression-free survival was 9.3 in the carboplatin/paclitaxel only cohort versus 17.9 months among 41 patients undergoing primary treatment with carboplatin/paclitaxel/trastuzumab in those with stage III or IV disease ($P=0.013$; HR, 0.40; 90% CI 0.20–0.80) and 6.0 versus 9.2 months, respectively, among 17 patients with recurrent disease ($P=0.003$; HR, 0.14; 90% CI 0.04–0.53). Therefore, the greatest benefit of trastuzumab was seen in those treated upfront. Notably, toxicity was not different between treatment arms, and no unexpected safety signals emerged. These encouraging results prompted changes in the National Comprehensive Cancer Network Uterine Cancer Guidelines that trastuzumab in addition to platinum and

taxane-based chemotherapy is the preferred regimen for women with advanced or recurrent, HER2-positive uterine serous carcinoma [25[■]]. An updated overall survival analysis from this trial is forthcoming.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 IN OVARIAN CANCER

HER2 overexpression in ovarian cancer has been investigated in observational and retrospective studies, but data are mixed with regards to the prognostic role of the biomarker in this setting. However, as observed in breast, gastric, and endometrial cancer, several contemporary reports demonstrate that the expression of HER2 is a poor prognostic factor in ovarian cancer. In a recent metaanalysis of 34 studies that included over 5180 ovarian cancer patients, of women with ovarian cancer, HER2 expression was associated with worse progression-free and overall survival [40[■]]. Thirty-four studies that included 5180 ovarian cancer patients were collected for analysis, and expression of HER2 was negatively correlated with clinical prognosis of overall survival (HR = 1.57, 95% CI 1.31–1.89, $P < 0.001$) and progression-free survival (HR = 1.26, 95% CI 1.06–1.49) in ovarian cancers.

Only limited studies exist studying the role of anti-HER therapy in ovarian cancer, almost all preclinical studies or small, retrospective case reports or series. In a preclinical study of patient-derived xenograft models with HER2-positive ovarian cancer, HER2-targeted therapy resulted in significant inhibition of tumor growth compared with untreated controls [41[■]]. However, the responses in each case were inferior to those to chemotherapy, even for chemoresistant lines. When chemotherapy and HER2-targeted therapy were administered together, a significant regression of tumor was observed after six weeks of treatment compared with chemotherapy alone. Another study of HER2-positive cell lines trastuzumab-DM1 possessed promising antitumor effects on HER2-overexpressing ovarian cancer in a mouse model, which provided valuable references for the future clinical trials [42]. Additionally, a retrospective, nonrandomized study by Yang *et al.* [43] demonstrated that in 80 patients with recurrent ovarian cancer treated with either single-agent trastuzumab versus trastuzumab and abraxane [43]. The partial response rates of the combined medication group and the single medication group were 45.9 and 44.2%, respectively. There were no complete response rates, and overall survival was equivalent in both groups (7.0 versus 7.3 months, $P = 0.63$). HER2 status was not reported. Clearly, additional studies are needed to identify those ovarian cancer patients who will potentially most benefit from anti-HER2 therapies.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 IN CERVICAL CANCER

Although much of the focus of HER2 in gynecologic malignancies has focused on type II endometrial cancers, ERBB/HER2 mutations and amplifications are found frequently in cervical carcinoma. In the cancer genome atlas report of 228 cases, the rate of HER2 amplification was 17% and more common in adenocarcinoma compared with squamous cell carcinoma [44]. In a more recent study that performed whole-exome sequencing on 69 cervical cancer specimens, 5.8% of tumors had mutations in the extracellular domain of

ERBB2 and cell lines with these ERBB2 mutations showed sensitivity to the HER inhibitors afatinib and neratinib [45[■]].

Clinic trial data in cervical cancer patients is limited. Lapatinb was evaluated as monotherapy and in combination in second-line recurrent or advanced cervical cancer. Unfortunately, median overall survival was 39.1 weeks for lapatinib monotherapy with a low-response rate of only 5% [46]. Tumor HER2 status was not measured, which may, in part, explain the low response rate.

In a genomically targeted basket trial, neratinib monotherapy was studied in patients with a variety of tumor types all harboring ERBB2 mutations. Of five patients with ERBB2 mutated cervical cancer, three had a clinical benefit (including one partial response) and therefore enrollment of this cohort is ongoing [47[■]].

OVERCOMING RESISTANCE TO HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 THERAPY

Despite promising clinical activity, resistance to HER2-targeted therapy may ultimately develop [48]. The main mechanisms of resistance could be categorized into four groups [48,49]:

1. Heterogeneity of HER2 expression within the tumor [50]
2. Alterations in the binding site of HER2 and extracellular domain shedding [51]
3. Activation of downstream signals by other concurrent mutations (PI3K gain of function mutation, PTEN loss of function mutation, cyclin E1 gene amplification) so that blocking HER2 has no effect [30,52,53]
4. Overexpression of other HER family receptors [54]

Mechanisms of resistance to HER2-targeted therapy in gynecologic cancer have best been studied in uterine serous carcinoma. Among the four groups listed above, heterogeneity of HER2 expression is the leading cause of resistance to HER2-targeted therapies in uterine serous carcinoma, leading to over-growth of HER2-negative cells. In contrast to breast cancer, where HER2 is homogeneously overexpressed, over 50% of the 3+ positive USC samples show significant heterogeneity by IHC (i.e., variability of tumor staining within cells in the same tumor) [50]. These findings not only provide potential molecular explanation for the failure of previous clinical trials targeting endometrial cancer with single-agent trastuzumab [38] but also explain the rationale for combining HER2 therapy with chemotherapy in these heterogeneous tumors.

Another strategy that might demonstrate activity against heterogeneous tumors could be the use of the new conjugated forms of monoclonal antibodies directed at HER2. These new drugs show activity not only against tumor antigen-positive target cells but also against tumor antigen-negative surrounding cells through a bystander effect [55]. SYD985 (Synthon Biopharmaceuticals) is an example of a new class of ADC that is composed of trastuzumab linked to a highly potent DNA-alkylating agent, duocarmycin, with a cleavable linker. It showed promising preclinical activity against USC cell lines and xenografts with strong (3+)

as well as low-to-moderate (1+/2+) HER2/neu expression [56]. Further clinical trials are warranted to investigate its clinical effects.

Resistance due to alterations in the binding site of HER2 and extracellular domain shedding could be overcome by use of irreversible pan HER inhibitors, such as afatinib and neratinib [57,58]. They act by inhibiting all four HER receptors leading to inhibition of downstream pathways [59]. However, a downstream gain of function mutation in PI3K may also occur that would lead to development of resistance to these agents [52]. In-vivo data demonstrated a strong and long-lasting tumor growth inhibition when a PIK3CA inhibitor (GDC-0032, taselisib) is used in combination with neratinib in USC models overexpressing HER2 [60].

Finally, expression of other HER family members, specifically HER3 has been shown to confer resistance to anti-HER2 therapy in breast and other malignancies [61]. Anti-HER2 therapy leads to upregulation of HER3 expression which then causes dimerization of HER2 and HER3 [62]. This HER2/HER3 dimer can no longer bind trastuzumab, thereby making it resistant to such therapy. To counteract this dimerization process, dual therapy binding two different epitopes of HER2 (trastuzumab and pertuzumab) was found to be highly active in preventing HER2/HER3 dimerization in breast cancer leading to improved clinical outcomes [63]. The synergistic activities of pertuzumab with trastuzumab against primary USC cell lines overexpressing HER2 have also been demonstrated [64]. These preclinical results in USC, as well as positive trials in breast cancer, strongly support the design of clinical trials that investigate the dual targeting of HER2 in patients with USC.

CONCLUSION

Alterations in HER2 signaling through overexpression, gene amplification, and gene mutations represent a promising target for the development of new therapeutic options for patients with gynecologic malignancies. Patients with uterine serous carcinoma have high rates of HER2 overexpression, and a poor prognosis (including high rates of recurrence even with early-stage disease) and therefore represent an ideal population to target for HER2-directed therapy. Phase II data have demonstrated an improvement in survival with the addition of trastuzumab to standard therapy in women with advanced disease. This represents a promising first step in the addition of targeted therapy to the treatment of rare gynecologic malignancies – a paradigm that has been relatively stagnant for the past decade. Breast cancer trials have demonstrated improved responses to dual agent as well as sequential anti-HER2 therapy. Preclinical data suggest these strategies may also be effective against uterine serous and cervical cancer. Translating these findings into clinical trials is imperative to improve the cancer outcomes of women with these aggressive gynecologic malignancies.

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KEY POINTS

- The role of HER2 and other EGFR family members as prognostic markers and therapeutic targets are well established in breast cancer and other solid tumors.
- A significant portion of type II uterine cancers and cervical cancers as well as a small number of ovarian cancers harbor alterations in HER2 and other downstream pathways. Thus, HER2-targeting agents hold promise as monotherapy or combination therapy in well-selected patients.
- The addition of trastuzumab, a HER2-targeting agent, to chemotherapy, improves survival in select women with HER2-positive advanced and recurrent uterine cancer.
- Further clinical trials are needed to establish the role of HER2-targeted therapy (including pan-HER and dual agent therapy) in other HER2 gynecologic oncology populations, such as early-stage type II uterine cancer, cervical cancer, and ovarian cancer.

Table 1.

Nomenclature for the EGFR/ERBB family

Members of the EGFR/ERBB protein family	Other common names
HER1	EGFR, ERBB1
HER2	ERBB2, CD340, protooncogene neu
HER3	ERBB3
HER4	ERBB4

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Table 2.**FDA-approved HER2-targeting agents**

Drug	Class	Mechanism	FDA approval
Trastuzumab	Monoclonal antibody	Binds the extracellular domain of HER2	HER2+ metastatic breast cancer and adjuvant therapy for high-risk breast cancer HER2+ metastatic gastric cancer
Pertuzumab	Monoclonal antibody	Binds to a extracellular domain of HER2 (different epitope than trastuzumab)	HER2+ breast cancer (neoadjuvant, metastatic and early stage) in combination with trastuzumab and chemotherapy
Lapatinib	Tyrosine kinase inhibitor	Inhibits HER1 and HER2	HER2+ metastatic breast cancer in combination with capecitabine after progression on trastuzumab HER2+ hormone receptor positive metastatic breast cancer in combination with letrozole
Neratinib	Tyrosine kinase inhibitor	Inhibits HER1, HER2, and HER4	HER2+ early-stage high-risk breast cancer (extended adjuvant therapy after trastuzumab)
Afatinib	Tyrosine kinase inhibitor	Inhibits HER1, HER2, and HER4	Select EGFR mutated metastatic NSCLC as well as progressive squamous NSCLC with select EGFR mutations
Ado-trastuzumab emtansine	Antibody drug conjugate	Trastuzumab and a microtubule inhibitor DM1	HER2+ breast cancer with residual disease after neoadjuvant therapy that included trastuzumab

EGFR, Epidermal growth factor receptor; *HER*, human epidermal growth factor receptor; *NSCLC*, non-small cell lung cancer.