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Review Article

Targeting HER-2/Neu in serous endometrial cancer: A review

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Abstract

Serous endometrial cancer is a clinically aggressive type of uterine cancer, responsible for a disproportionate incidence of advanced stage disease, recurrences and deaths. Serous endometrial cancers are characterized by alteration of p53, STK15, p16, and HER2. The purpose of this review is to describe the current understanding of the role of the HER-2/neu pathway in the carcinogenesis of serous endometrial cancer, to explore the rationale for, and efficacy of targeting the HER-2/neu receptor in the treatment of these tumors.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with over 50,000 cases diagnosed annually, resulting in approximately 8,000 deaths [1]. Endometrial cancer is classically categorized as type I or type II tumors, corresponding to endometrioid and non-endometrioid histologic types, respectively. A majority of endometrial cancers are type I, which are often well differentiated, confined to the uterus, cured with hysterectomy, and associated with excellent prognosis [2]. Type II tumors include serous and clear cell histologic types, and they tend to be clinically aggressive tumors that are associated with advanced stage at diagnosis and chemo resistance. Despite comprising only, a minority of all endometrial cancers, type II tumors are responsible for a disproportionate percentage of endometrial cancer-related recurrences and deaths [3-6]. Secondary to the poor outcomes associated with serous endometrial cancer, novel targeted therapies that are effective are needed.

Serous endometrial cancers are characterized by alteration of p53, STK15, p16, and HER2. The purpose of this review is to describe the current understanding of the role of the HER-2/neu pathway in the carcinogenesis of serous endometrial cancer, to explore the rationale for, and efficacy of targeting the HER-2/neu receptor in the treatment of these tumors.

HER-2/neu pathway

HER-2 (also termed ErbB2) is a member of the Epidermal Growth Factor Receptor (EGFR) family. These are a group of transmembrane growth factor receptors with tyrosine kinase activity, which activate a variety of second messenger systems and downstream signaling pathways which regulate cell proliferation, migration, survival and differentiation [7,8]. The EGFR receptors initiate signaling after dimerization with other EGFR members in response to ligand binding. The mechanisms by which HER-2 induces transformation and promotes tumorigenesis is not fully elucidated. Proposed mechanism includes: PI2Kinase/Akt activation, src kinase activation, and upregulation of cyclin d1 and degradation of p27, regulators of the cell cycle [9-14]. In addition to other pathways being activated, there is also extensive crosstalk between pathways. It is likely that tumorigenesis represents the culmination of a multitude of aberrations in and amongst various pathways and signals. While much of the research implicating HER-2/neu in tumor development is in breast cancer, these may represent driver mutations in other malignancies, including endometrial cancer.

Prognostic significance of HER-2/neu expression in serous endometrial cancer

The prognostic significance of HER-2 expression in endometrial cancer has been investigated in retrospective studies. In an evaluation of endometrial cancer specimens from nearly 250 patients treated at the Mayo Clinic, Hetzel et al noted "strong" HER-2/neu IHC staining in 15% [15]. This HER-2/neu over expression was associated with a worse Progression-Free Survival (PFS) and Overall Survival (OS). Only a minority of specimens evaluated were non-endometrioid histology. In a study of nearly 500 patients with endometrial cancer, including 58 with serous histology, Morrison et al noted a relatively high rate of HER2 expression and amplification, 43% and 29%, respectively, when compared to well-differentiated endometrioid type tumors [16]. Patients with tumors which overexpressed and/or demonstrated HER2 amplification, had a worse PFS and OS. This association with HER-2 positivity and worse outcomes persisted when evaluating only grade 3 tumors. Researchers from Mayo Clinic and UCLA also noted

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a higher incidence of HER2 positivity in type II tumors compared to type I endometrial cancers (17% versus 1%) [17]. However, in patients with type II cancers, this HER-2 amplification was not statistically significantly associated with a worse overall survival (18 months versus 29 months, P=0.113). Slomovitz et al. in their study of uterine papillary serous cancer, noted a similar incidence of HER-2 overexpression (18%) in uterine papillary serous carcinoma specimens [18]. However, in their study, HER-2 overexpression was associated with a poorer overall survival (18 months versus 48 months, P value 0.008). Diaz-Montes and colleagues at Johns Hopkins, in their analysis of 25 patients with uterine serous carcinoma, reported a worse survival associated with HER-2/neu overexpression. However, this association was most likely secondary to the advanced stage at diagnosis associated with HER-2/neu positivity versus HER-2/neu negative status (75% stage III or IV versus 15% stage III or IV, respectively) [19]. A more recent post hoc analysis of HER-2 overexpression and gene amplification of tumor samples came from the Gynecologic Oncology Group (GOG) 177, a prospective randomized trial comparing doxorubicin and cisplatin versus doxorubicin, cisplatin and paclitaxel in patients with advanced and/or recurrent endometrial cancer. In this study, HER-2 overexpression was more common in serous tumors (61% versus 41%) while HER-2 amplification was not more common in serous tumors [20]. There was no clear evidence that women with HER-2 amplified or overexpressed tumors had an improved survival with the addition of paclitaxel to cytotoxic doublet therapy, although the power to detect clinically meaningful differences was low.

HER-2/neu targeted therapy in endometrial cancer

There are clinical trials evaluating the efficacy of HER-2/neu targeted therapy in endometrial cancer. GOG 229D was a phase II trial evaluating lapatinib, a dual inhibitor of EGFR and HER-2 tyrosine kinase activity, in 30 patients with persistent or recurrent endometrial cancer, including 7 patients with serous carcinoma [21]. HER-2/neu expression was rare (12% of pre-treatment biopsies). Twenty-one patients had progressive disease, one was indeterminate for response, one had a partial response, and 7 had stable disease. This lack of clinical activity was concluded to be, at least in part, explained by the unselected patient population, i.e. lacking HER-2 expression. The GOG has investigated trastuzumab, a HER-2/neu targeted monoclonal antibody, as a single agent in the treatment of advanced or recurrent endometrial cancer in a phase II trial [22]. Women with stage III, IV or recurrent endometrial cancer were treated with weekly trastuzumab until progression or unacceptable adverse effects. Tumors were required to have HER2 overexpression (initially in trial) or HER-2 amplification. Of 33 eligible patients treated, 18 had increasing disease, 12 had stable disease, and 3 were indeterminate for tumor response. Median progression free survival was less than two months. In contrast, there are reports of clinical responses in patients with recurrent endometrial cancer [23-25].

These inconsistencies are likely attributable to several factors across studies. One such factor is the relative rarity of serous histology, making it difficult to establish a large enough study to reach statistical significance. Another is the histologic heterogeneity of tumors and the means of determining HER-2 positivity. Furthermore, it has also been difficult to weigh the impact on prognosis of various risk factors, individually and synergistically. Overall, there has been a lack of effective therapies and the consequent historically short duration of responses in advanced and recurrent endometrial cancer highlights the difficulty in assessing responses to new therapies as well as the need for new treatment approaches.

Defining HER2 'positivity' in serous endometrial cancer

Laboratory evaluation of HER2 overexpression and amplification, and its association with response to trastuzumab, are well established for invasive breast cancer. Early trials of trastuzumab were performed exclusively on women with HER-2 overexpression by immunohistochemistry [26,27]. This testing modality was chosen based on studies of gene amplification by Southern blot hybridization, which showed strong correlation with HER2 overexpression [28]. Response in this subset of women was favorable, with a reduced recurrence and mortality. Criteria for HER-2 immunohistochemically evaluation in these early trials was graded semi quantitatively as 0, 1+, 2+, and 3+, with 2+ and 3+ being considered HER2-positive and thus eligible for the given trial. Importantly, subsequent retrospective analysis of these patients showed that only women with 3+ overexpression or HER2 gene amplification saw benefit from trastuzumab [29]. Laboratory evaluation of HER2 in invasive breast cancer has become commonplace in determining if a woman is eligible for treatment with trastuzumab. Acceptable testing methods include immunohistochemistry and in situ hybridization. To promote consistency in testing among laboratories, The American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) have developed guidelines for HER2 evaluation, first in 2007 and most recently in 2013 [30,31]. Current (2013) guidelines for immunohistochemistry state HER2 expression is to be graded as 0, 1+, 2+, or 3+, similar to grading in the early trials. In short, 0 shows no expression, 1+ weak discontinuous membranous expression, 2+ weak but complete membranous expression in >10% of cells, and 3+ strong complete membranous expression in >10% of tumors cells. Results of 0 and 1+ are considered negative, 3+ positive, and 2+ equivocal. Equivocal results are reflexed to amplification testing, which may be done by fluorescence in situ hybridization (FISH) or chromogeneic in situ hybridization. By either modality, HER2:CEP17 >2.0 is considered positive for amplification, as is >6 HER2 signals per cell. Laboratories may also omit immunohistochemically testing, and opt for ISH as first line testing.

Approximately 20% of invasive breast cancers are HER2-positive [32,33]. A majority of HER2-positive cases of invasive breast cancer exceed the minimal laboratory thresholds. By immunohistochemistry, 3+ cases generally show striking expression in the cell membranes of nearly all tumor cells. High-level gene amplification (HER2:CEP17 $\geq$ 5) is present in ~50% of HER2-positive cases overall, and >75% of cases with 3+ HER2 overexpression [32]. Amplification level correlates with expression level. Agreement between immunohistochemistry and in situ hybridization is high. Current standards dictate >95% concordance should be seen between immunohistochemistry positive/negative results and in situ hybridization results [31].

The laboratory experience with HER2 testing in serous endometrial carcinoma has been more challenging. In a genomic characterization of endometrial cancer specimens, including 66 serous types, by the Cancer Genome Atlas Research Network, 25% of serous or serous-like tumors had HER-2 amplified with protein overexpression [34]. Most studies have been small (range: n=3 to 108), because of the rarity of the disease (reviewed in [35]). Studies have shown 14-65% of cases are HER2-positive by immunohistochemistry, though comparison is limited by differing criteria and small patient numbers for several series. HER2 amplification rates are also variable, being identified in 0-71% of cases, though the largest studies have shown amplification in 10-35%.

The largest studies offer somewhat contradictory evidence,

and bear discussion. Using tissue microarrays constructed from 75 high grade serous endometrial carcinomas, Xu et al showed 12% had HER2 overexpression by immunohistochemistry and 12% had HER2 amplification by FISH [36]. Concordance between immunohistochemistry and FISH was high, with discrepancy seen in only 5% of cases. Criteria for immunohistochemistry positivity was considered 2+ and 3+. Of cases with HER2 amplification by FISH, 67% had HER2:CEP17 >2.2, though the exact ratios were not reported. In a separate tissue microarray study on 69 high grade serous endometrial carcinomas, Mentrikoski et al. similarly showed 13% of women had HER2 amplification by FISH [37]. However, overexpression was considerably higher in this study, seen in 40% of cases using 2013 ASCO/CAP guidelines. Despite this lack of concordance, 100% of tumors showing HER2 amplification had 3+ overexpression. In a retrospective review of whole tissue sections on 108 endometrial serous and mixed serous/endometrioid carcinomas, Buza et al. showed 35% of evaluable cases had HER2 amplification by FISH, and 23% showed HER2 overexpression using 2013 ASCO/CAP criteria [38]. Concordance between FISH and immunohistochemistry was 86%.

The reasons for the contradictions in the studies above are challenging to decipher. The studies by Xu et al. and Mentrikoski et al. both used limited tissue microarray material, and found similar rates of HER2 amplification [36,37]. HER-2 overexpression differed significantly between these studies, possibly resulting from the different criteria used for immunohistochemically evaluation. It is striking, however, that both studies showed HER-2 overexpression in the vast majority of tissues harboring HER-2 amplification. The study by Buza et al showed differences in HER-2 amplification from both of these studies, though comparison is difficult because this study was performed on whole tissue sections. This increase in evaluated tissue area likely increased the analytical sensitivity for cases showing focal amplification. Intratumoral heterogeneity for HER-2 amplification and overexpression may thus explain some of the discrepancy. Although the study by Metrikoswki et al. was performed on tissue microarray materials, intratumoral heterogeneity was further investigated on whole tissue sections in cases found to have HER2 amplification [37]. These showed intratumoral heterogeneity for both expression and amplification in 33% of HER-2-amplified cases. Overexpression and amplification tended to occur in tandem. The study by Buzz et al (performed on whole tissue sections) similarly showed heterogenous HER-2 protein expression in 31% of all cases. The same group has also shown HER-2 amplification tends to occur in tandem with HER-2 overexpression in cases with heterogenous expression [39]. The study by Mentrikoski et al also identified six cases that overexpressed HER-2 and had trisomy 17, without amplification of HER-2. These cases suggest polysomy may be a source of HER2 overexpression, and therefore a marker of response to trastuzumab.

The studies cited above highlight important details regarding immunohistochemistry and FISH testing in high grade serous carcinomas, particularly in comparison to the experience with invasive breast cancer. First, serous endometrial carcinomas with HER-2 amplification tend to show strong HER-2 overexpression. However, the pattern of HER-2 overexpression appears to differ between serous carcinoma and invasive breast cancer. While invasive breast cancers categorized as 3+ by immunohistochemistry tend to have strong membranous expression in the majority of tumors cells, high grade serous carcinomas are more prone to focal strong expression, which would be considered 3+ by current ASCO/CAP guidelines. This may not correspond to amplification in many cases. It has also been shown that endometrial serous carcinomas frequently have a strong but incomplete membranous staining pattern, with no expression in the luminal aspect of the cell [38]. Such cases would not be considered positive by current ASCO/CAP criteria, but may be associated with HER-2 amplification. HER-2 expression in gastric and gastroesophageal adenocarcinoma has shown a similar pattern of expression, which is recognized in current protocols for this tumor site [40,41]. Future protocols for endometrial serous carcinoma may include such cases as positive, though further study will be required. Second, intratumoral heterogeneity for HER-2 amplification and overexpression appears to be common in endometrial serous carcinomas, and may explain many of the contradictory findings in larger studies. This should be considered in laboratory testing for patient selection for inclusion in future trials of trastuzumab in treating endometrial serous carcinoma.

Based on the summation of data, it is the opinion of the authors of this review that HER-2 copy number evaluation is the better test to evaluate high grade endometrial serous carcinoma for inclusion in future trials. It is also imperative that future trials perform HER-2 testing on multiple areas of the tumor, in order to account for intratumoral heterogeneity of HER-2 amplification and overexpression.

Conclusions

Serous endometrial cancer is a clinically aggressive type of uterine cancer, responsible for a disproportionate incidence of advanced stage disease, recurrences and deaths. Currently available cytotoxic chemotherapies yield short-lived responses with significant systemic toxicities. Novel, effective, targeted therapies are needed. Considering the relatively frequent HER-2/neu alterations in serous endometrial cancer, its negative prognostic implications, and the success of trastuzumab in breast cancer, targeting HER-2/neu in serous endometrial cancer represents a plausible and attractive treatment strategy. However, this promise has not yet been delivered. Herein, we have detailed the role of HER-2/neu in serous endometrial cancer, its potential role as a prognostic indicator, the difficulties in determining HER-2 positivity, and the outcomes of HER-2/neu targeted monotherapy (lapatinib, trastuzumab). If the full potential of HER-2/neu-directed therapy in serous endometrial cancer is to be realized, these factors must be accounted for and future trials must select patients with HER-2/neu positive tumors, as defined by rational, uniform criteria, be adequately powered to detect a meaningful response, and consideration given to incorporation of HER-2/neu monoclonal antibodies to standard platinum-based chemotherapy rather than use as a single agent.

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