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Novel membrane-based targets – Therapeutic potential in gynecological cancers

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Contents

1. Introduction 294
2. Epidermal growth factor receptor inhibitors 294
   2.1. Early trials in unselected patients disappointing results 294
   2.2. Next generation epidermal growth factor receptor inhibitors 294
      2.2.1. Pertuzumab 294
      2.2.2. MM121 295
   2.3. The future of HER targeting in gynecological cancers 295
3. Insulin growth factor-like receptor-1 (IGF1R): an old target new drugs 296
   3.1. Relevance of the IGF1R axis to gynecological tumors 296
   3.2. IGF1R antibodies in gynecological cancers 296
   3.3. Tyrosine kinase inhibitors (TKIs) of IGF1R and insulin receptor 296
4. Targeting MET 296
   4.1. MET: relevance in gynecological cancers 296
   4.2. Lessons from other tumor types 296
   4.3. Multitargeted MET inhibitors in gynecological cancers 297
5. The fibroblast growth factor receptor family (FGFR) 297
6. NOTCH receptor 297
7. Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) receptors 298
8. Drug immunoconjugates 299
   8.1. Folate receptor-α (FRα) 299
   8.2. Luteinizing hormone releasing hormone (LHRH) receptors 299
   8.3. Anti –NaPi2b – monomethyl auristatin E (MMAE) 300
9. Conclusion 301
   Conflict of interest 301
   Reviewers 301
   References 301
   Biography 303

Abstract

Recent advances have been made in the molecular profiling of gynecological tumors. These discoveries have led to the development of targeted therapies that have the potential to disrupt molecular pathways involved in the oncogenesis or tumor progression. In this review, we highlight areas of recent progress in the field of membrane receptor inhibitors in gynecological malignancies and describe the biological rationale underlying the inhibition of these receptors. We will introduce drug immuno-conjugates, and give an update on the biological

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rationale and the clinical studies involving agents directed against EGFR, HER3, IGFR, MET, FGFR, NOTCH, and TRAIL. We also discuss the challenge facing these new therapies.

Keywords: Targeted therapies; Membrane receptor inhibitors; Gynecological malignancies

1. Introduction

Thanks to recent large-scale molecular profiling studies in ovarian [1], endometrial [2] and cervical [3] cancers, such as the integrated genomic analyses performed by the Cancer Genome Atlas (TCGA) network, significant headway has been made in the molecular profiling of gynecological malignancies. Unfortunately these advances have not yet translated into meaningful clinical benefit for patients. Over the last two decades, clinical trials with epidermal growth factor receptor (EGFR) inhibitors conducted in women with gynecological cancers have been resoundingly negative [4]. However, there may be cause for optimism. Therapeutic strategies aimed at novel membrane-based targets are being investigated and may offer real hope for the future of membrane receptor inhibitors in gynecological malignancies.

This review will present an update of inhibitors of novel membrane-based targets at various stages of clinical development in gynecological cancers such as agents directed against HER3, HER2-containing heterodimers, as well as the receptors for MET, Folate, Fibroblast growth factor, Notch or Trail (tumor-necrosis-factor related apoptosis-inducing ligand). The therapeutic potential of drug immuno-conjugates targeted to membrane based tumor associated antigens in gynecological oncology will also be introduced. Finally, the biological rationale for specific membrane receptor inhibitors in molecularly selected gynecological tumors will be addressed, and some of the challenges facing these new therapies will be discussed.

2. Epidermal growth factor receptor inhibitors

2.1. Early trials in unselected patients disappointing results

EGFR was identified several decades ago as an attractive target in gynecological tumors because of its frequent overexpression [5]. Unfortunately a number of clinical trials conducted in women with ovarian, endometrial or cervical cancers failed to demonstrate any clinical activity for either antibodies or small molecule inhibitors of EGFR [6–8].[4]. Results of trials targeting the human epidermal growth factor receptor 2(HER2) receptor were also disappointing [9].

One explanation frequently proposed to account for the observed lack of activity is that these trials were conducted in an unselected population. Given the observation that a significant proportion of type I endometrial cancers (EC) demonstrate significant HER2 overexpression or amplification [10], one study of trastuzumab was conducted in advanced endometrial cancer with HER 2+/3+ or *HER2* amplification by FISH (fluorescent in situ hybridization). No objective responses were observed among the 18 patients with documented *HER2* amplification [11].

HER2 amplification is relatively common (18.2%) in ovarian mucinous carcinomas although not necessarily of prognostic significance. Response to conventional therapy is limited in this histologic subtype of OC and trastuzumab may provide a treatment option for patients with mucinous carcinoma when the tumor has HER2 amplification and overexpression [12].

2.2. Next generation epidermal growth factor receptor inhibitors

In the last 10 years, an improved understanding of the structure, function and interaction between individual epidermal growth factor receptors has led to the identification of new therapeutic strategies [13]. EGFR, HER3 and HER4 require ligand for activation and undergo homo- or heterodimerization with another partner. HER2 has no ligand, and its activation occurs via homo-dimerization in the setting of significant HER2 overexpression, or because the receptor is recruited to heterodimerize with another family member (Fig. 1).

2.2.1. Pertuzumab

Pertuzumab was developed as an antibody that could interfere with HER2-containing heterodimers. As such it may have activity in HER2 non-amplified cancers driven by HER2 containing heterodimers and/or high levels of circulating HER ligands. Although pertuzumab can no longer truly be qualified as a ‘novel’ therapy since it has now received Federal Drug Administration (FDA) approval in HER2+ breast cancer [14], the novelty is investigating its activity in non-HER2 amplified cancers.

A first phase II trial suggested that the benefit of pertuzumab might be limited to patients with putatively activated HER2 signaling as measured by phosphorylated HER2 levels [15]. A follow-up study randomized patients with advanced platinum resistant ovarian cancer to gemcitabine alone or in combination with pertuzumab and the investigators sought to explore efficacy in the subset with activated HER2 signaling–as measured by gene expression levels of *EGFR*, *HER2*, *HER3* and their ligands. Again no benefit