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Advances in anti-angiogenic agents for ovarian cancer treatment: The role of trebananib (AMG 386)

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Contents

Abstract

Ovarian cancer is a multifaceted and genomically complex disease and has emerged as leading cause of death among gynecological malignancies. Gold-standard treatment consisted of cytoreductive surgery and paclitaxel–carboplatin chemotherapy. Recently, promising results of randomized trials have definitively confirmed the importance of angiogenesis in oncogenesis and ovarian cancer behavior, by showing a significant prolongation of progression-free survival with the addiction of an angiogenesis inhibitor to standard treatment in the first and second line setting. Research over the years has sequentially provided a rapidly broadening signaling landscape and many drugs targeting different signaling pathways of angiogenesis have been developed and investigated. Recently accumulating scientific evidence has started to shed light on the efficacy of AMG 386, a new peptibody reported to neutralize the interaction between angiopoietins (Ang1/2) and their Tie2 receptors, thus representing a promising alternative, both in terms of efficacy and toxicity profile and is considerably under investigation. The aim of this review is to summarize the recent researches and clinical progresses of AMG 386 as a novel target agent in ovarian cancer.

Keywords: AMG 386; Trebananib; Angiopoietin; Anti-angiogenesis; Ovarian cancer; Targeted therapy; Peptibody

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1. Introduction

Although tremendous breakthroughs have been made in improving and deepening our understanding about multifaceted nature of ovarian cancer in last decade, it still remains the most aggressive type of gynecological malignancy. Worldwide estimation published in 2011 [1] reported an incidence of 225,500 new cases of ovarian cancer, with 140,200 deaths per year; of these, 100,300 new cases and 64,500 annual deaths arise in the developed countries. Five years overall survival rates for localized, regional and distant ovarian cancers are currently estimated to be 90%, 75% and 30%, respectively [2]. Current gold standard of treatment includes cytoreductive surgery combined with platinum-based chemotherapy. Disease staging at time of surgery is crucial for tailoring appropriate patient management while optimal surgical debulking is the most powerful prognostic factor impacting on patients' survival [3]. It has been estimated that each 10% increase in the proportion of patients undergoing complete cytoreductive surgery is associated with a 3.0 month increase in median overall survival time and with an improved outcome to subsequent adjuvant therapy [4]. However the median PFS for ovarian cancer patients is still up to 18 months, despite the surgical efforts in reducing residual tumor and the high response rate up to 75% to first-line platinum-based chemotherapy [5].

During the last years, thanks to the growing knowledge of cancer biology, researchers have concentrated their efforts in developing new strategies for ovarian cancer treatment. The most promising approaches include immunotherapy and molecular targeted therapies. The last ones have been engineered to interfere with specific processes associated with oncogenesis, such as proliferation, adhesion, invasion and angiogenesis. In this context cancer neo-angiogenesis is considered as a crucial process for cancer growth and survival and therefore a big panel of new molecules, interfering with different pathways of tumor neo-vascularization, is currently under investigation.

2. Background: Tumor angiogenesis and role of angiopoietins

As above mentioned, tumor angiogenesis is critical for transition from the avascular phase to the vascular phase, playing a pivotal role in tumor growth and progression. In the absence of neovascularization, most solid tumors stop growing when they are 2–3 mm in size and enter a dormant stage [6].

The main pathway involved in tumor angiogenesis is modulated by VEGF (Vascular Endothelial Growth Factor) family and its triggers and receptors. Due to the high levels of intratumoral VEGF [7], target therapies binding VEGF represent one of the most promising molecular drugs in ovarian cancer in last years. More recently, attention has focused on the distinct roles of the angiopoietin family, and their receptor tyrosine kinase, in vascular remodeling and stabilization [8–12].

The four angiopoietins (Ang1, Ang2, Ang3, Ang 4) share with VEGF family members the characteristic of being largely specific for the vascular endothelium. Ang1, predominantly produced by vascular mural cells and Ang2, produced by endothelial cells, are the most studied angiopoietins [13]. Ang4, almost exclusively expressed in lung, is relatively poorly characterized, while Ang3 is the mouse orthologue of Ang4 [14].

Angiopoietin (Ang) 1 and 2 are key endothelial cell selective growth factors. All of which act as ligand for endothelial cell specific tyrosine kinase receptor Tie2 [15]. Tie1 and Tie2 are endothelial cell specific receptors expressed in vascular and lymphatic endothelial cells. Up to now, there is no ligand identified for Tie1 receptor [16].

Ang1 binding to Tie2 receptor promotes blood vessel stability by enhancing interactions between perivascular cells and endothelium, enhancing endothelial cell survival and leading to a more stable vasculature with decreased permeability [17]. Ang2 interferes Ang1-mediated vessel normalization, resulting in impaired pericyte coverage, vessel destabilization, and increased vascular permeability [18]. Pericyte loss and abnormal vasculature was found to be associated to Ang2 overexpression, which seems to be strictly connected with tumor angiogenesis and growth [19,20].

Furthermore, significant correlation was also observed between VEGF and Ang2 mRNA expression in human ovarian cancer stroma endothelial cells, but not between VEGF and Ang1 or Tie2, although Ang2 was only detected in 12% of tumor samples [21], speculating that VEGF interaction with the angiopoietin-Tie2 axis supports angiogenesis during tumor growth. VEGF can promote proteolytic processing and shedding of the extracellular domain of Tie-2, suggesting that loss of VEGF might increase availability of this receptor [22]. These observations raised the possibility that Ang-1/Tie-2 activation may function to support tumor vasculature in the specific context of VEGF blockade. Interesting, Ang1/Tie2 activation prevents vessel regression and promotes tumor survival during antiVEGF treatment supporting a model in which activation of Tie-2 is important for tumor and vessel survival when VEGF-dependent vasculature is stressed [23].

3. Non-angiopoietin anti-angiogenic strategies in ovarian cancer

Several types of angiogenesis inhibitors have been evaluated in ovarian cancer including monoclonal antibodies targeting VEGF (bevacizumab) or VEGFR2 (IMC 1121B, ramucirumab), soluble VEGFR decoy receptors targeting circulating VEGF (VEGF Trap, aflibercept), or tyrosine kinase inhibitors (TKIs) binding VEGFR and/or PDGFR and/or