ELSEVIER

Critical Reviews in Oncology/Hematology 84 (2012) 224–242

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Turning promise into progress for antiangiogenic agents in epithelial ovarian cancer

Arne R.M. van der Bilt [a,b], Elisabeth G.E. de Vries [a], Steven de Jong [a], Hetty Timmer-Bosscha [a], Ate G.J. van der Zee [b], Anna K.L. Reyners [a,*]

[a] *Department of Medical Oncology, University of Groningen, University Medical Center Groningen, The Netherlands*
[b] *Department of Gynecological Oncology, University of Groningen, University Medical Center Groningen, The Netherlands*

Accepted 16 March 2012

Contents

Abstract

Despite efforts to improve chemotherapeutic efficacy in epithelial ovarian cancer, outcome for patients with advanced disease has remained unchanged since the introduction of standard carboplatin and paclitaxel. Interest has therefore shifted toward molecularly targeted therapies that interfere with important features of ovarian carcinogenesis, such as angiogenesis. Several angiogenesis inhibitors, targeting vascular endothelial growth factor (VEGF) ligands (bevacizumab, VEGF-Trap) or their receptors (VEGFR-targeted tyrosine kinase inhibitors) have been clinically evaluated. These agents demonstrated efficacy in phase II clinical trials. Results from phase III trials, in which bevacizumab was added to standard frontline chemotherapy, show a modest effect. Although the initial expectations for angiogenesis inhibitors have been

Keywords: Ovarian cancer; Angiogenesis; Antiangiogenic therapy; Bevacizumab; Tyrosine kinase inhibition; VEGF-Trap; Patient selection

* Corresponding author at: Department of Medical Oncology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. Tel.: +31 050 3611543; fax: +31 050 3614862.
E-mail address: a.k.l.reyners@umcg.nl (A.K.L. Reyners).

1040-8428/$ – see front matter
doi:10.1016/j.critrevonc.2012.03.006

tempered, further research is warranted to define their precise place in the treatment of ovarian cancer. This review summarizes the performed and ongoing studies with regard to angiogenesis inhibitors in ovarian cancer, and the available data on biomarkers for response prediction. Preclinical studies evaluating alternative angiogenesis inhibitors will also be discussed.

1. Introduction

Epithelial ovarian cancer is the sixth most common form of cancer in women in developed countries. Patients commonly present with disease that has disseminated beyond the ovaries, due to the absence of symptoms in early stage disease. Despite tumor response rates of more than 80% to frontline therapy, consisting of surgical debulking and chemotherapy, chemoresistant recurrences are common and result in a poor overall survival (OS) rate of ovarian cancer patients [1,2].

A carboplatin–paclitaxel doublet is the standard frontline chemotherapy since the past decade. Various chemotherapeutic regimens, including the addition of cytotoxic drugs to standard chemotherapy, failed to show therapeutic superiority [3,4]. Moreover, no effective treatment has been established for platinum refractory ovarian cancer. This has raised interest in targeted drugs that interfere with characteristic phenomena relevant to ovarian cancer biology.

Several antiangiogenic drugs are currently in advanced stages of clinical development. Ovarian cancers are highly angiogenic and belong to the few cancer types in which even monotherapy with antiangiogenic drugs has antitumor activity [5]. Recent phase III results with the vascular endothelial growth factor (VEGF) neutralizing antibody bevacizumab, added to standard frontline chemotherapy, have tempered initial expectations [6,7]. Here, we present the currently available data on the efficacy of angiogenesis inhibitors in ovarian cancer.

2. Angiogenesis

Angiogenesis is the process during which new capillaries arise from pre-existing vessels. In humans, the turnover of vascular endothelial cells (vECs) is low and vessels are quiescent in most healthy adult tissues, whereas angiogenesis is mostly associated with pathological conditions such as cancer [8]. This differential requirement for angiogenesis in health and disease offers a window for antiangiogenic therapy [8].

2.1. Angiogenic signaling

For an extensive description of (cancer) angiogenesis we refer to excellent reviews published on this subject [8,9]. In brief, angiogenesis generally refers to sprouting angiogenesis (Fig. 1) [10]. During this process new vessel sprouts are formed by vECs that make up the endothelial lining of capillaries and post-capillary venules. These vECs loosen their intercellular contacts, proliferate and migrate toward the angiogenic signal, forming a solid cord of cells.

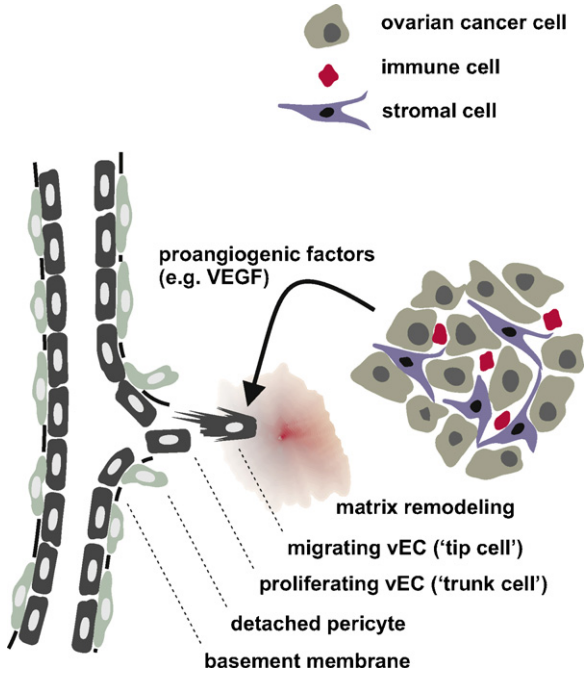

Fig. 1. In sprouting angiogenesis, some of the vECs incorporated into established vessels are activated by proangiogenic factors (*e.g.* VEGFA) produced by both cancer cells and accessory cells (stromal and immune cells). These activated endothelial cells (tip cells) detach from the vascular structure and migrate towards the growth factor gradient. Remodeling of the extracellular matrix through the actions of matrix metalloproteases (MMPs) facilitates their migration. Following the highly motile tip cells are other endothelial cells, called trunk cells, which have the capacity to proliferate and form the new vessel sprout.

Fragile immature capillaries arise after lumen formation, with vessel walls that only consist of endothelium [10]. Pericytes are recruited to this endothelial lining, establishing direct cellular contacts with the vECs and – together – produce the basement membrane that envelops the matured capillary.

Angiogenesis involves the actions of stimulatory and inhibitory cytokines [9]. These cytokines stem from cancer cells as well as stromal and blood cells. VEGF family members are key-drivers of many steps throughout the angiogenic process, from the initial induction of vascular permeability to endothelial cell proliferation, migration and survival [11]. VEGF family members differentially bind to three cognate VEGF receptors (VEGFRs) which are present on the (lymph)vascular endothelium (Fig. 2). Signaling *via* VEGFR2 is considered the mainstay of angiogenesis. VEGFR3 contributes to both angiogenesis and lymphangiogenesis [12]. The exact function of VEGFR1 is still subject of debate. At least in part, it serves as a decoy receptor, consistent with its soluble variant sVEGFR1 [13]. Taken