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Antiangiogenic agents in gynecological cancer: State of art and perspectives of clinical research

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Abstract

Vascular endothelial growth factor [VEGF] pathway, which plays a key role in angiogenesis, may be blocked by either extracellular interference with VEGF itself (bevacizumab [BEV] or aflibercept), or intracytoplasmic inhibition of VEGF receptor (pazopanib, nintedanib, cediranid, sunitinib and sorafenib). An alternative approach is represented by trebananib, a fusion protein that prevents the interaction of angiopoietin [Ang]-1 and Ang-2 with Tie2 receptor on vascular endothelium. The combination of antiangiogenic agents, especially BEV, and chemotherapy is a rational therapeutic option for primary or recurrent ovarian carcinoma. However, it will be difficult to accept that it represents the new standard treatment, until biological characterization of ovarian carcinoma has not identified subsets of tumors with different responsiveness to BEV. Anti-angiogenesis is an interesting target also for recurrent cervical or endometrial cancer, but nowadays the use of anti-angiogenic agents in these malignancies should be reserved to patients enrolled in clinical trials.

Keywords: Epithelial ovarian cancer; Cervical cancer; Endometrial cancer; Bevacizumab; Molecular signatures; Pazopanib; Nintedanib; Trebanabib

1. Introduction

Dysregulation of angiogenesis plays a major role in tumor growth and metastatic spread, and therefore inhibition of angiogenesis is a promising therapeutic strategy for several malignancies, including gynecological cancers [1–9]. To grow beyond microscopic size, tumors need an angiogenic switch to enter a vascular phase in which blood perfusion provides a better delivery of oxygen and nutrients and an enhanced disposal of waste products [10]. Vascular endothelial growth factor [VEGF] family, which is important for the start of neoangiogenesis, consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, placental growth factor [PlGF], VEGF-E and VEGF-F members [11–13]. VEGF binding sites include three receptor tyrosine kinases, termed VEGF receptor [VEGFR]-1, VEGFR-2, and VEGFR-3, that are expressed in most human solid tumors [14–17]. Bevacizumab [BEV] is a humanized monoclonal antibody that neutralizes all major isoforms of VEGF, thereby preventing VEGFR binding and inhibiting endothelial cell proliferation and vessel formation [18]. This agent, first approved by the US Food and Drug Administration [FDA] for combination therapy with fluorouracil-based regimens for metastatic colorectal cancer, has been subsequently employed in different malignancies, such as breast cancer, non-small cell lung cancer, renal cancer, and epithelial ovarian cancer [7,8,19–21]. Aflibercept is a recombinant fusion protein that consists of portions of VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human immunoglobulin G1, and that functions as a decoy receptor able to bind VEGF-A, VEGF-B and PIGF [22,23]. Aflibercept has been tested in several human tumors with contrasting results [24–27].

If VEGF has a key role in the early events of angiogenesis, other factors, such as fibroblast growth factor [FGF], platelet-derived growth factor [PDGF], angiopoietin [Ang]-1 and Ang-2, are involved in the maintenance of neovascularization [5,28–31]. Therefore, different anti-angiogenic agents have been developed and tested in experimental and clinical settings.

Phase II and III clinical trials have evaluated several oral, small-molecule tyrosine kinase inhibitor [TKI]s and a fusion peptibody (trebananib) in patients with different malignancies.

Pazopanib is a multi-targeted TKI, with activity against VEGFR-1, VEGFR-2, VEGFR-3, PDGF receptor [PDGFR]-α, PDGFR-β, and c-kit [32], approved for the treatment of renal cancer [33] and soft tissue sarcoma [STS]s [34]. Nintedanib targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, FGF receptor [FGFR]-1, and FGFR-3 [35]. This agent has been tested in non-small cell lung cancer [36] and colon cancer [37]. Cediranid, which binds to VGFR-1, VEFR-2, VGFR-3, PDGFR, and c-Kit [38], has been used in non-small cell lung cancer [39], gastrointestinal stromal tumors [GIST]s [40], STSs [40], and glioblastoma [41]. Sunitinib is a multi-targeted TKI of VEGFR, PDGFR, c-KIT, FLT3, colony-stimulating factor 1 [CSF-1], and RET [42], approved for renal cancer [33], imatinib-resistant GISTs [43], and pancreatic neuroendocrine tumors [44]. Sorafenib is an inhibitor of VEGFR-2, VEGFR-3, PDGFR-β, B-RAF and c-Kit [45], employed in the first-line treatment of advanced hepatocellular carcinoma [46] and in the second-line treatment of renal cancer [33]. Ang-1 and Ang-2 are endothelial-secreted proteins which interact with the Tie2, a receptor tyrosine kinase primarily expressed in the vascular endothelium, and which enhance neoangiogenesis [47,48]. Moreover, Ang-1 can contribute to stabilization of newly produced vessels through activation of anti-apoptotic pathways mediated by AKT and survivin in endothelial cells. Trebananib is a recombinant peptide-Fc fusion protein that inhibits angiogenesis by preventing the interaction of Ang-1 and Ang-2 with Tie2 [49]. In tumor xenograft models, dual inhibition of Ang-1 and Ang-2 was associated with greater suppression of angiogenesis and tumor growth compared with single inhibition of either ligand. Therefore trebananib can represent a very