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Clinical pharmacology of anti-angiogenic drugs in oncology

P. Gougis[a,b,c,d,e,*], J. Wassermann[e], J.P. Spano[e,f], N. Keynan[b], C. Funck-Brentano[a,b,c,d], J.E. Salem[a,b,c,d]

[a] INSERM, CIC-1421 and UMR ICAN 1166, F-75013 Paris, France
[b] AP-HP, Pitié-Salpêtrière Hospital, Department of Pharmacology and CIC-1421, F-75013 Paris, France
[c] Sorbonne Universités, UPMC Univ Paris 06, Faculty of Medicine, F-75013 Paris, France
[d] Institute of Cardiometabolism and Nutrition (ICAN), F-75013 Paris, France
[e] Department of Medical Oncology, Groupe Hospitalier Pitié-Salpêtrière, University Pierre and Marie Curie (Paris VI), Institut Universitaire de Cancérologie, AP-HP, Paris, France
[f] Institut Pierre Louis d'Epidémiologie et de Santé Publique UMR S 1136, F-75013 Paris, France

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ABSTRACT

Abnormal vasculature proliferation is one of the so-called hallmarks of cancer. Angiogenesis inhibitor therapies are one of the major breakthroughs in cancer treatment in the last two decades. Two types of anti-angiogenics have been approved: monoclonal antibodies and derivatives, which are injected and target the extracellular part of a receptor, and protein kinase inhibitors, which are orally taken small molecules targeting the intra-cellular Adenosine Triphosphate –pocket of different kinases. They have become an important part of some tumors' treatment, both in monotherapy or in combination. In this review, we discuss the key pharmacological concepts and the major pitfalls of anti-angiogenic prescriptions. We also review the pharmacokinetic and pharmacodynamics profile of all approved anti-angiogenic protein kinase inhibitors and the potential role of surrogate markers and of therapeutic drug monitoring.

1. Introduction

Due to their enlarged and tortuous vessels, Hippocrates compared the cross section of tumors to crab claws. This observation would explain the name "carcinos" that he reportedly gave to this disease, which was later translated to the Latin word "cancer". Judah Folkman (Folkman et al., 1971) first provided an explanation for this vasculature, isolating what he called tumor angiogenesis factor. Falkman later proposed the inhibition of this angiogenesis factor as a treatment. Tumor cells need oxygen and nutrients to grow, and passive diffusion only happens at scales of less than a millimeter. Therefore, angiogenesis is a key process for a macroscopic tumor, one of the so called hallmarks of cancer (Hanahan and Weinberg, 2000). In the last couple of decades, the development of drugs targeting angiogenesis through inhibition of vascular endothelial growth factors (VEGF) and their receptors (VEGFR), led to an important change in the oncology field. Although they are targeting the same pathway, two different categories of drugs were developed: monoclonal antibodies (MABs) and their derivatives, which are VEGF(*R*)-selective drugs administered intravenously and protein kinase inhibitors (PKIs), which are given orally (Figs. 1 and 2). PKIs are small molecules able to inhibit intracellular signal transduction. Kinases have a phosphorylation activity that regulates survival and proliferation of cellular processes. PKIs inhibit a wide spectrum of kinases and are not specific to VEGF and/or its receptor (Fig. 3). They have a different spectrum of action and adverse effects depending on the kinases they inhibit. PKIs have a narrow therapeutic index. Hence, knowing basic pharmacological concepts, drug interactions and management of PKIs toxicity improves the quality of patient care. In this review, we discuss the pharmacological particularities of angiogenesis inhibitors, their indications, and their clinical management.

2. Clinical pharmacology

2.1. Pharmacological targets

2.1.1. VEGF/VEGFR pathway

VEGF/VEGFR pathway is one of the major pathways in angiogenesis. The VEGF family consists of five members: VEGF-A, B, C, D and Placental Growth Factor (Roskoski, 2017). VEGFR family consists of three members: VEGFR-1 (i.e, Fms Like Tyrosine kinase FLT-1, gene name *FLT1)* and VEGFR-2 (i.e, Kinase insert Domain Receptor KDR,

* Corresponding author at: Centre d'Investigation Clinique Paris-Est, Groupe Hospitalier Pitié-Salpêtrière, University Pierre and Marie Curie (Paris VI), AP-HP, Paris, France.
E-mail address: paul.gougis@aphp.fr (P. Gougis).

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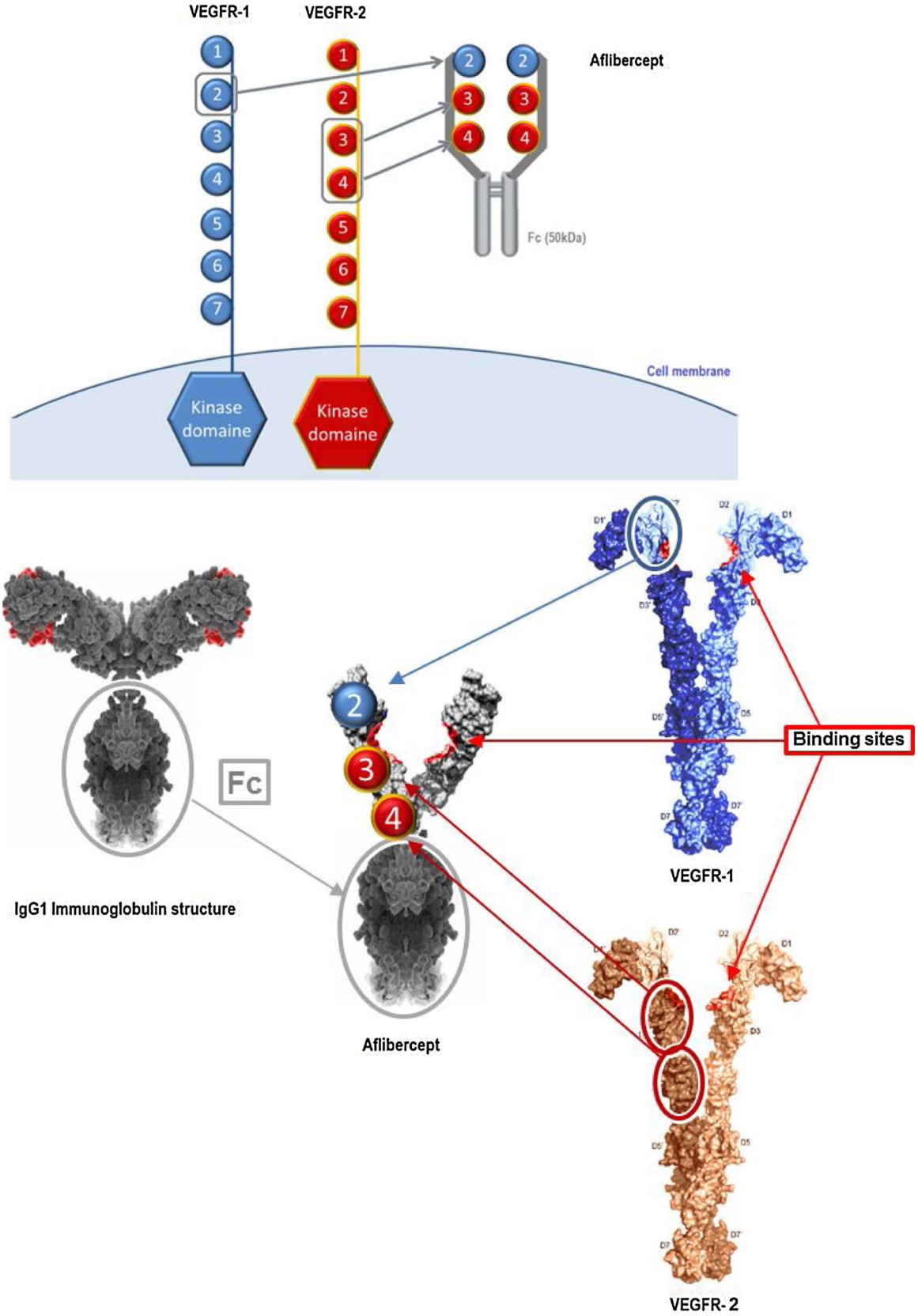

Fig. 1. Aflibercept structure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Aflibercept is the product of the combination of Vascular Endothelial Growth Factor (VEGF) receptor-1 domain 2; of VEGF receptor-2 domain 3 and 4 and of the Fc part of an immunoglobulin. Aflibercept can bind with a high affinity to circulating VEGF-A, VEGF-B and PlGF which are both VEGFR-1 and VEGFR-2 ligands. Binding sites are shown in red.
Abbreviations: Fc: crystallizable fragment; IgG: immunoglobulin type G; PlGF: Placental Growth Factor; VEGFR: vascular endothelial growth factor;