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REVIEW OF CLINICAL USE OF MONOCLONAL ANTIBODIES (BEVACIZUMAB)

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ABSTRACT

Bevacizumab is a humanized monoclonal antibody that has several potentials as a single agent or in combination with a chemotherapeutic agent. The first used in metastatic colorectal cancer (mCRC) therapy, metastatic breast cancer (mBC) therapy, and non-small cell lung cancer (NSCLC) therapy. Furthermore, there is evidence of clinical use for antiangiogenic therapy, as assessed by endothelial cell proliferation and tubule formation and widely accepted as first-line therapy in combination with chemotherapy. Due to the clinical validation of bevacizumab as a specific inhibitor of the interaction between VEGF-A and VEGFR2, the increasing number of monoclonal antibodies in development has targeted VEGFR2 as a promising molecular target for anti-angiogenesis.

KEYWORDS: Bevacizumab, monoclonal antibodies, VEGF-A, VEGFR2, and angiogenesis**.**

INTRODUCTION

Bevacizumab is a humanized monoclonal antibody (93% human, 7% murine sequences–molecular weight 149 kDa) that target vascular endothelial growth factor A (VEGF-A) a key mediator in the angiogenesis of cancer cells and was the first monoclonal antibody to be approved for use in the treatment of colorectal cancer by health Canada which was produced at Genentech using hybridomas generated from mice immunized with the 165-residue form of recombinant human vascular endothelial growth factor (rhuVEGF 165) conjugated with keyhole limpet hemocyanin.[1]

VEGF is a family comprised of seven members VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-F, and P1GF which are soluble diffusible glycoproteins all of which have a common

VEGF homology domain.[2] VEGF is a major regulator of angiogenesis during normal and pathological processes, including that associated with tumor growth.[3] VEGF-A isoform binds into two VEGF tyrosine kinase receptors, the VEGFR1, and VEGFR2, both of which are two downstream receptor proteins that share a similar structure. The binding of VEGF-A to either of these receptors results in the activation of downstream pathways which lead to endothelial cell proliferation and migration.[4]

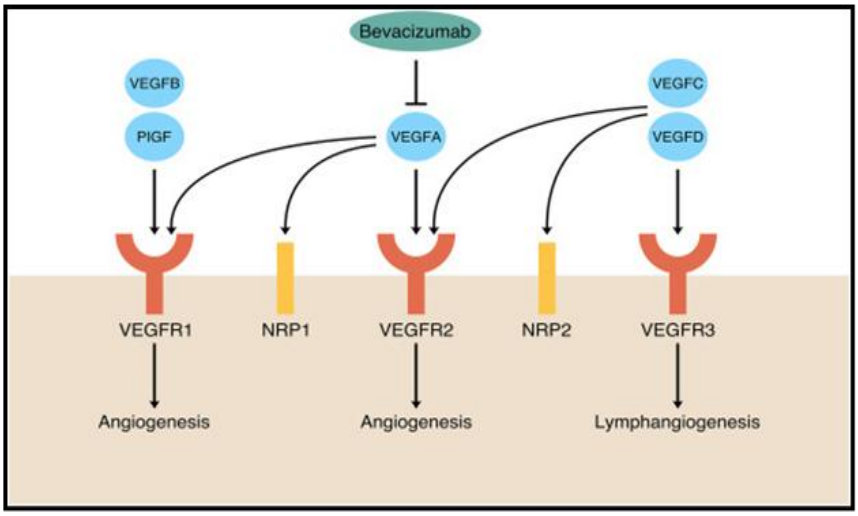

Figure 1: Mechanism action of bevacizumab.[14,15]

Proliferation and migration result in the formation of new tubular structures which mediated the development of new blood vessels from pre-existing ones, providing cancer cells with oxygen and nutrients which promote tumor growth.[4] Due to the strong relationship between VEGF and angiogenesis, VEGF serum levels have often been used as a surrogate biomarker for angiogenic activity in cancer patients.[5] The clinical use program for bevacizumab comprises trials in different diseases: antiangiogenic and colorectal cancer. The clinical study of all conformed and analyzed based to the guidelines.[5]

Drug Targeting

Despite the wide range of clinical usefulness of bevacizumab for cancer therapy, the identification of novel angiogenic therapeutic targets and development of novel drugs as alternative or combination treatments. In the present article, we review monoclonal antibodies (VEGF-A) being developed for clinical use as antiangiogenic therapy and meta-colorectal cancer. The mechanism of action of monoclonal antibodies showed in Figure 1.

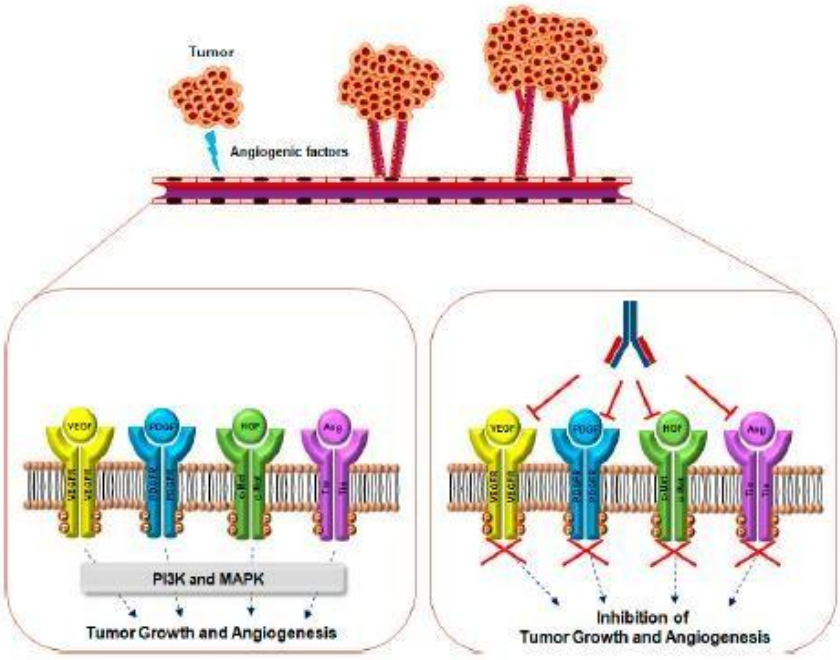

Figure 2: Mechanism of action of monoclonal antibodies targeting VEGF, PDGF, HGF, Ang and their receptors for suppressing tumor growth and angiogenesis.[6]

The mechanism of action of therapeutic antibodies is being developed for anti-angiogenic therapy. Under pathological conditions, including hypoxia, most tumor cells and/or adjacent cells upregulate the expression of many angiogenic factors, including VEGF, PDGF, HGF, and Ang, and secrete them within the tumor microenvironment. When these molecules bind their cognate receptors, receptor dimerization and autophosphorylation stimulate downstream signaling molecules including phosphatidyl inositol-4,5-biphosphate 3-kinase (PI3K)/v-Akt murine thymoma viral oncogene (Akt) and MAPK (dash lines) for the promotion of tumor growth and angiogenesis. Currently, most antibody therapeutics are being developed to block the interaction between agonists and their receptors (T arrows).[6]

VEGF signaling is one of the major signaling pathways required for embryonic vascular development and angiogenesis. VEGF- A, VEGF-B, and P1GF are constitutive VEGFR-1 agonists that induce migration and proliferation. In endothelial cells and macrophages, VEGFR-1 initiates migration by stimulating the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/Akt-Rac 1 pathway through a receptor for activated protein kinase C1. PI3K pathway activation by VEGFR-1 is also linked to endothelial cell proliferation and tubulogenesis.[6]

VEGF-A activation of VEGFR-2 initiates PLC interaction with the Tyr1175 residue of internalized VEGFR-2 in early endosome antigen 1-positive endosomes.[7],[8] This leads to subsequent cascades that activate Ca2+-dependent rapidly accelerated fibrosarcoma (RAF)-mitogen-activated protein kinase (MEK)-ERK1/2 and calmodulin-calcineurin-nuclear factor of activated T cells pathways, which promote endothelial cell migration, proliferation, and homeostasis. Interaction of T-cell-specific adaptor protein with VEGFR-2 leads to the activation of Akt signaling, which determines endothelial cell shape, adhesion, survival, and vessel permeability.[6]–[8] In addition, Akt activation by VEGFR-2 stimulates endothelial nitric oxide synthase, inducing the release of NO into the extracellular space, which promotes vasodilation in adjacent smooth muscle cells.[6],[7]

Preclinical Studies

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to all isoforms of and neutralizes the biological activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with the complementary determined regions of the humanized murine antibody that binds to VEGF. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149 kD.[6]

Bevacizumab binds to vascular endothelial growth factors and thereby inhibits the binding of VEGF to its receptors on the surface of endothelial cells. Neutralizing the biological activity of VEGF reduces the vascularization of tumors, thereby inhibiting tumor growth.[9] The binding epitope of bevacizumab has been defined by crystal structure analysis of a complex Fab ligand.[3],[10]

In an early preclinical study in 1997, some reported of humanized of the murine anti-VEGF. The pharmacokinetic properties of bevacizumab in several species have been previously described and are consistent with a typical humanized monoclonal antibody. Bevacizumab inhibits the growth of human tumor cell lines in nude mice, achieving a maximal inhibition at the dose of 1–2 mg/kg twice weekly.[3],[11]

Half-maximal inhibition required 0.1–0.5 mg/kg doses. The magnitude of the inhibition is inversely related to the content of stromal-derived mouse VEGF within the tumor xenograft. In tumors with a high human/mouse VEGF ratio, the inhibition can exceed 90%.[12],[13] For a recent review of the preclinical studies with bevacizumab, as a single agent and in combination with cytotoxic agents.[3]

Safety evaluation studies of bevacizumab were conducted in Macaca fascicularis (cynomolgus monkey).[3],[14] Bevacizumab is expected to have pharmacologically active in this species, considering the complete identity between human and cynomolgus VEGF isoforms at the protein level.[3],[15] Following administration of bevacizumab, a young adult cynomolgus monkey exhibited a physical dysplasia characterized by an increase in hypertrophy of the growth plate, very similar to the growth plate lesion observed in mice treated with Flt (1-3)-IgG.[16] ther expected effects of prolonged bevacizumab administration were suppression of angiogenesis in the female reproductive tract, resulting in decreased ovarian and uterine weights and an absence of corpora lutea.[3],[14]

Clinical studies

In 1997, Genentech initiated Phase I clinical trials with bevacizumab. It was provided by the Health Department of Canada. The Phase I studies showed that the antibody as a single was relatively nontoxic therefore adding it into standard chemotherapy regimens did not significantly exacerbate chemotherapy-associated toxicities.[3]

In 1998, several Phase II studies were initiated with bevacizumab in different tumor types, either as a single agent or in combination with chemotherapy. Bevacizumab was combined with standard first-line chemotherapy in metastatic colorectal cancer and stage IIIb/IV non-small cell cancer (NSCLC). The most encouraging efficacy results were seen when bevacizumab was combined with chemotherapy in colorectal and non-small cell cancer and when used as a single agent in renal cell cancer. The Phase II renal cell trial was a randomized, double-blind, placebo-controlled trial of single-agent bevacizumab in subjects with metastatic renal cell cancer.[3]

Bevacizumab was given at doses of 3 mg/kg and 10 mg/kg every two weeks. There was a significant prolongation of the time to progression of disease in the high-dose antibody group as compared with the placebo group. The Phase II colorectal trial was a randomized, open-label, study to evaluate the efficacy and safety of bevacizumab combined with 5FU/leucovorin in subjects with previously untreated metastatic colorectal cancer. A total of 104 subjects were randomized to the three treatment arms: 36 subjects to the 5-fluorouracil (FU)/leucovorin alone arm, 35 subjects to 5-FU/leucovorin + 5mg/kg/2 week bevacizumab.[3]

Venous thromboembolism was the most significant adverse event. Hypertension, proteinuria, and epistaxis were other potential safety concerns. Relative to single chemotherapy, an

increase in time to progression and survival was observed in the two bevacizumab arms. Interestingly, patients in the lower dose bevacizumab arm did better than those in the higher dose arm. This finding is at variance with the renal cell trial, which showed a dose-responsive enhancement of efficacy. The reason for this difference is not clear and may reflect some imbalances in randomization that resulted in more patients with poor prognostic factors in the high-dose arm.[3]

During the conduct of this Phase II trial, the addition of irinotecan to bolus 5fluorouracil/leucovorin (IFL regimen) was shown to prolong survival and was considered to be the new standard first-line treatment for metastatic colorectal cancer in the United States. For this reason, the control chemotherapy in the Phase III study was chosen to be the IFL regimen. The Phase III colorectal trial was a large, randomized, double-blind, active-controlled, three arms, Phase III study to evaluate the efficacy and safety of bevacizumab in combination with bolus-IFL chemotherapy or 5-FU/leucovorin chemotherapy as the first-line therapy for previously untreated metastatic colorectal cancer.[3]

Patients (total of 923) were randomized into the three treatment arms in this study: 411 subjects in Arm 1 (bolus IFL+ placebo), 402 subjects in Arm 2 (bolus IFL+ bevacizumab), and 110 subjects in Arm 3 (5FU/leucovorin+bevacizumab). Enrollment in the third arm was discontinued early when the data monitoring committee assessed that the safety profile of IFL + bevacizumab was acceptable. Bevacizumab was administered at the dose of 5 mg/kg once every two weeks. The addition of bevacizumab to bolus-IFL resulted in a significant increase in overall survival, with a 34% reduction in the hazard of death. The clinical benefit of bevacizumab was seen in all prespecified subject sub-groups, including those defined by age, sex, performance status, location or primary tumor, number of organs involved, and duration of metastatic colorectal cancer. On February 26, 2004, bevacizumab was approved by the FDA as a first-line treatment for metastatic colorectal cancer.[3]

Clinical Use as Antiangiogenic therapy

So far, Avastin (Bevacizumab), an antibody against VEGF has been the only antiangiogenic drug to be approved by the FDA. Yet, in comparison with chemotherapy, its effect is indirect (inhibition of VEGF) and not necessarily lethal. At optimal conditions, endothelial cells may survive without VEGF. VEGF protected endothelial cells from apoptosis caused by serum withdrawal. In the presence of serum, withdrawal of VEGF did not cause apoptosis.[9]

Bevacizumab, an anti-VEGF antibody, was recently developed as cancer therapy to suppress tumor angiogenesis. The mechanism was a recombinant humanized immunoglobulin G (IgG) monoclonal antibody that targets VEGF-A and inhibits the formation of the VEGF-A and VEGFR-2 complex. Due to the clinical validation of bevacizumab as a specific inhibitor of the interaction between VEGF-A and VEGFR2, the increasing numbers of monoclonal antibodies in development have targeted VEGR2 as a promising molecular target for anti-angiogenesis.[6]

Angiogenesis is a physiological process in which new blood vessels are formed from preexisting vessels. It occurs during normal growth and development, as well as during wound healing. Under physiological conditions, angiogenesis is tightly regulated by the complex and coordinated actions of pro-angiogenic and anti-angiogenic factors according to the spatiotemporal requirements of cells or tissues. Tumor angiogenesis is a hallmark of cancer and plays a crucial role in providing oxygen and nutrients to tumor cells during cancer progression and metastasis.[6]

Clinical Use as Metastatic Colorectal Cancer (mCRC) therapy

The current data on the management of colorectal cancer indicate that angiogenesis and its inhibition are key factors. Bevacizumab remains the most important and well-studied drug among the known antiangiogenic agents. The use of bevacizumab (Avastin, Roche Pharma AG) has been widely accepted as first-line therapy in the management of advanced colorectal cancer in combination with other classic chemotherapy agents such as 5-fluorouracil (5-FU) or novel agents.[17],[18]

This combination improves the response rates to treatment, progression-free survival, and overall survival, in patients with advanced disease, as opposed to chemotherapy alone. Currently, the combination of the novel targeted therapy agents irinotecan, capecitabine and bevacizumab are the most widely used in metastatic colorectal cancer resulting in increased response rates. Bevacizumab is the first agent to affect survival in patients with metastatic colorectal cancer, improving survival by 30%. Furthermore, it has been established as the first and second-line therapy for this cancer, due to its advantages compared with routine chemotherapy, which includes less resistance and toxicity. Its beneficial effect has been proved in phases II and III clinical trials.[17],[18]

The usual dose of bevacizumab is 5 mg/kg BW every two weeks in combination with other chemotherapeutic agents such as irinotecan and 5-fluorouracil/leucovorin (LV). It is administered by intravenous (IV) injection which must last 90 min initially and is gradually reduced to 60 min and 30 min, IV bolus injection is contraindicated. Bevacizumab has been used postoperatively 6 weeks after colorectal cancer resection for the management of synchronous liver metastasis at a dose of 5 mg/kg BW every 2 weeks or 7.5 mg/kg BW every 3 weeks. The usual dose of bevacizumab is 5 mg/kg BW every 2 weeks for 5 cycles and even the uncommon dose of 10 mg/kg BW has been combined with 5-FU/LV or capecitabine in advanced colorectal cancer.[17]

Recent trials have confirmed the effectiveness of bevacizumab in combination with other chemotherapeutic agents in metastatic colorectal cancer showing its increasing application in clinical practice. A large randomized multicenter controlled trial showed that the addition of bevacizumab to capecitabine plus or minus mitomycin significantly improved progression-free survival (PFS) without inducing further major toxicity, only expected modest adverse events including proteinuria, hypertension, arterial thromboembolism, and the hemolytic uremic syndrome were observed.[17]

CONCLUSION

Bevacizumab was used in preclinical and clinical studies as a single agent or in combination with chemotherapeutic agents. Furthermore, there is evidence of clinical use for antiangiogenic therapy, as assessed by endothelial cell proliferation and tubule formation and widely accepted as first-line therapy in the management of advanced colorectal cancer. Due to the clinical validation of bevacizumab as a specific inhibitor of the interaction between VEGF-A and VEGFR2, the increasing numbers of monoclonal antibodies in development have targeted VEGFR2 as a promising molecular target for anti-angiogenesis. However, there are rare, although serious side effects and toxicities should be considered. This novel biological agent is generally beneficial and well-tolerated.

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