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Bevacizumab

Oncolytic

Prop INN

anti-VEGF MAb
Avastin™

Immunoglobulin G_1 (human-mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer

CAS: 216974-75-3

EN: 223839

Abstract

The role of angiogenesis in the growth and metastasis of tumors is well established. Research has therefore focused on developing agents that target angiogenic factors such as vascular endothelial growth factor (VEGF) in order to inhibit tumor growth. One such agent is bevacizumab, a humanized monoclonal antibody generated by engineering the VEGF binding residues of a murine neutralizing antibody into the framework of a normal human immunoglobulin G (IgG). Bevacizumab recognizes VEGF receptors 1 and 2 (VEGFR-1 and VEGFR-2) and thus can neutralize the biologically active forms of VEGF that interact with these receptors. Bevacizumab has shown antiangiogenic and preclinical antitumor activity and was chosen for further development as a treatment for breast cancer and colorectal cancer.

Introduction

Angiogenesis is a complex process defined as the formation of new blood vessels from preexisting vessels. It is essential for embryogenesis and embryonic development and under normal physiological conditions in adults, angiogenesis is under stringent spatial and temporal control and only occurs during tissue repair, ovulation and endometrial regulation. Mediators of angiogenesis include the angiogenic cytokines such as vascular endothelial growth factors (VEGFs) and fibroblast growth factors (FGFs) which stimulate endothelial cells to secrete proteases and plasminogen activators. These in turn cause degradation of the vessel basement membrane, thus allowing cells to invade the surrounding matrix. Cells will then migrate, proliferate and eventually differentiate to form a new lumen-containing vessel. The endothelial cells subsequently deposit a new basement membrane and also secrete growth factors (*i.e.*, platelet-derived growth factor; PDGF) that attract supporting cells which, together with angiopoietins and ephrins, ensure and regulate stability of the new vessel (1, 2).

Many pathological conditions appear to involve persistent upregulation of the angiogenic process. These disorders include ischemic heart disease, atherosclerosis, psoriasis, rheumatoid arthritis, diabetic retinopathy, age-related macular degeneration and solid tumor growth, and they are all characterized by excessive angiogenesis resulting in development of vessels in an uncontrolled or disorganized manner (2-4). It is well accepted that tumor progression requires angiogenesis. Cancers are believed to lie dormant *in situ* until the fine balance between production of angiogenic stimulatory (*e.g.*, VEGF, FGF, PDGF) and inhibitory (*e.g.*, thrombospondins) factors has been disrupted causing an angiogenic switch (5). In fact, many tumor cell lines have been shown to secrete VEGF *in vitro* and VEGF mRNA is increased in most human tumors. Moreover, elevated serum levels of VEGF and FGF-2 have been detected in individuals with several tumor types (6). Thus, interference with VEGF and FGF action represents an attractive target for inhibition of angiogenesis which would be useful in a number pathologies, particularly cancer. A major problem arising during conventional cancer therapy is that tumor cells mutate frequently, resulting in resistance development. However, targeting of the more genetically stable endothelial cells instead of labile tumor tissue represents a treatment modality that is less prone to resistance development and inhibition of tumor-induced angiogenesis theoretically would be effective regardless of tissue type (7-10).

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There are several compounds which inhibit angiogenesis through a variety of specific mechanisms of action, including blocking matrix degradation (*i.e.*, matrix metalloproteinase inhibitors), blocking VEGF, FGF and PDGF receptor signaling, inhibiting normal endothelial cells and antagonizing integrin. The antiangiogenic therapeutic option of interfering with VEGF/VEGF receptor (VEGFR) interaction using VEGF or VEGFR antibodies is an attractive strategy. Because VEGF is a key mediator of neovascularization, research has intensely focused on interfering with the VEGF/VEGFR system in order to modulate angiogenesis. The VEGF family of ligands (43-46 kD glycoproteins) to date is composed of 6 members: VEGF-A (the first VEGF identified which includes 5 variants: VEGF-A_{121}, VEGF-A_{145}, VEGF-A_{165}, VEGF-A_{189} and VEGF-A_{206}), placenta growth factor (PlGF), VEGF-B, VEGF-C, VEGF-D and VEGF-E (from the orf parapox virus). Expression of VEGF is regulated by hypoxia which is evident during tumor progression and ischemia (11, 12). The activity of VEGFs is mediated through binding to specific cell surface receptors: VEGFR-1 (Flt-1), VEGFR-2 (also known as kinase insert domain-containing receptor [KDR] or Fms-like tyrosine kinase receptor 2 [Flt-2]) and VEGFR-3 (Flt-4). VEGFR-1 and VEGFR-2 are expressed predominantly on vascular endothelial cells while VEGFR-3 is expressed on lymphatic endothelium. VEGF receptor signal transduction is not clearly understood. Binding of the VEGFs to their receptors is known to induce homo- or heterodimerization of the ligand, which subsequently triggers intracellular autophosphorylation in their kinase domain. A cascade of signal transmissions eventually leads to the growth message in the cell nucleus (13-15).

There are 8 monoclonal antibodies that have been launched and more than 100 under development for cancer therapy. One such agent currently under development is bevacizumab (Avastin^{TM}), a humanized anti-VEGF monoclonal antibody generated by engineering the VEGF binding residues of the murine neutralizing antibody A.4.6.1 into the framework of the consensus human immunoglobulin G_1 (IgG_1) (16). Bevacizumab recognizes VEGFR-2 and VEGFR-1 receptors and thus binds and neutralizes all biologically active forms of VEGF that interact with these receptors (including VEGF-A_{165} and VEGF-A_{121}). Due to it antiangiogenic and preclinical antitumor activity, bevacizumab has been chosen for further development as a treatment for cancer.

Pharmacological Actions

The efficacy of bevacizumab against various cancer types has been demonstrated in several *in vivo* preclinical trials. A study using an i.p. ovarian carcinoma (OVCAR3) model in athymic mice showed that bevacizumab not only prevented ascites formation but also reversed preformed ascites associated with ovarian carcinoma. At the end of the study period, the volume of ascites in bevacizumab-treated (100 μg/kg) animals with developed ascites (abdominal circumference = 8 cm or larger with 5-10 ml ascites) was less than 1 ml as compared to 3-14 ml in vehicle-treated animals. Moreover, bloody ascites not seen in any of the bevacizumab-treated animals developed in 90% of the untreated animals. No significant differences in tumor burden were observed between treated and control animals (17).

A study using nu/nu mice bearing anaplastic thyroid cancer xenografts (ARO) allowed to implant for 1 week showed the efficacy of treatment with bevacizumab (200 mcg/day i.p. for 6 weeks) in significantly reducing tumors. Significant reductions in tumor growth were observed at 4, 5 and 6 (1.13 ± 0.26 *vs.* 2.77 ± 0.53 g in controls) weeks of treatment with bevacizumab. In addition, the tumors of 3 out of 9 bevacizumab-treated animals had central necrosis as compared to none of the tumors of control animals (18).

The efficacy of bevacizumab was shown to be enhanced against several human xenografts in combination with radiation or cisplatin. Tumor growth delays were examined after athymic Ncr/Sed nude mice bearing 6-mm human glioblastoma (U87) or human colon adenocarcinoma (LS174T) were treated with bevacizumab (6 injections of 100 mg/injection/mouse i.p. every 2 days) and administered single radiation treatments 24 h after the last injection. Growth delays of U87 tumors in animals treated with bevacizumab or radiation (20 or 30 Gy[a] or 30 or 40 Gy[h]) alone were 27 ± 9.2, 15 ± 8.2, 22 ± 9.2, 11 ± 4.5 and 22 ± 17.1 days, respectively, as compared to 45 ± 12.2, 77 ± 25.1, 49 ± 6.8, and 56 ± 11.6 days, respectively, in animals treated with a combination of the MAb and radiation. Similarly, growth of LS174T tumors were delayed 13 ± 3.6 and 9 ± 3.6 days in animals treated with the MAb alone or 20 Gy(a) alone, respectively, as compared to 36 ± 8.2 , 38 ± 14.1 and 38 ± 14.1 days in animals treated with the MAb in combination with 30 Gy(a), 30 Gy(h) and 40 Gy(h), respectively. From these results it was concluded that the growth effects seen with combination treatment including bevacizumab and 30 Gy(a) or 30 Gy(h) radiation were synergistic against U87 tumors and additive against LS174T tumors as compared to either treatment alone (19).

The tumor suppression seen with single-dose cisplatin (5 mg/kg on day 2) was shown to be enhanced when combined with bevacizumab (5 mg/kg i.p. twice weekly for 4 doses) in a study using nude mice bearing human non-small cell lung (CALU-6) tumors (pretreatment tumor size = 142 ± 7 mm^3). Treatment with a combination of the MAb and cisplatin resulted in a more than 50% significant suppression of tumor growth (tumor size = 964 mm^3) as compared to treatment with the MAb alone (1825 mm^3), cisplatin alone (2100 mm^3) and untreated controls (2600 mm^3) (20).

In addition to its anticancer efficacy, intravitreal bevacizumab (500 μg every 2 weeks) has been shown to be safe in a cynomolgus monkey model of laser-induced choroidal neovascularization. Choroidal neovascularization was induced by creating photocoagulation lesions (50 μm) in the maculae of animals on day 21 using an argon green laser (0.1 s, 350-700 mW). All eyes treated

with the MAb developed acute anterior chamber cells (1-4+) within 24 h of the first injection as compared to vehicle-treated eyes in which no inflammation was detected. However, inflammation of bevacizumab-treated eyes was transient, resolving within 1 week and subsequent intravitreal injections with the MAb resulted in less inflammation. When previously vehicle-treated eyes were injected with the MAb on day 42, development of 3-4+ anterior chamber cells was observed; a second administration of the MAb on day 56 resulted in less marked inflammation. It was concluded that treatment with bevacizumab in this model caused transient inflammation restricted to the anterior chamber which was resolved. No significant toxicity was observed with treatment (21).

The involvement of VEGF in follicular growth was demonstrated using bevacizumab to block angiogenesis in regularly cycling rhesus monkeys. Short-term treatment with the MAb (0.5 mg i.v. on 2 consecutive days during the late follicular phase) administered to animals following documentation of 2 normal ovulatory cycles, resulted in a significant lengthening of the follicular phase (21.3 ± 3.8 *vs.* 10 ± 0.7 and 9.8 ± 0.6 days in 2 normal, control ovulatory cycles). The rise in serum estradiol was suppressed by treatment on days 1 (67.2 ± 11.2 pg/ml), 2 (49.9 ± 7.5 pg/ml) and 3 (58.1 ± 7.6 pg/ml) as compared to the start of treatment (day 0 = 96.1 ± 6.0 pg/ml) and control days 1 (125.5 ± 20 pg/ml) and 2 (165.5 ± 24.9 pg/ml). Following the prolongation of the follicular cycle (ranging from 14-21 days), estradiol and LH levels were comparable to control cycles and all animals ovulated, had normal luteal function and had a normal posttreatment cycle. It was concluded that short-term treatment with bevacizumab successfully inhibited angiogenesis during the growth phase of the dominant follicle, thus interfering with its normal development (22).

Pharmacokinetics

The pharmacokinetics of i.v. and s.c. bevacizumab were examined in mice, rats and cynomolgus monkeys and the tissue distribution of [^{125}I]-labeled bevacizumab was investigated in rabbits. The clearance of bevacizumab following i.v. administration of 10 mg/kg was 15.7, 4.83 and 5.59 ml/day/kg in mice, rats and monkeys, respectively; the terminal half-life was 6-12 days in all species. The bioavailability of the MAb following s.c. administration was 69% in rats and 100% in mice and monkeys. Using the results obtained in these species, the serum clearance and terminal half-life of the agent in humans was predicted to be 2.4 ml/day/kg and 12 days, respectively. Tissue distribution studies in rabbits showed that radioactivity 2 h after i.v. injection of the radiolabeled MAb was mainly in plasma and to a lesser extent in highly perfused tissue like the kidneys, testes, spleen, heart and lungs; radioactivity was detected in plasma 48 h postdosing, with only minimal amounts detected in testes, bladder, heart, lungs and kidneys (23).

A study in cynomolgus monkeys administered bevacizumab (2-50 mg/kg for various durations) examined the population pharmacokinetics of the MAb using NONMEM. Results showed that clearance and central volume of distribution values were related to body weight so that a 30% change from median body weight resulted in a 30% change in clearance and a 24% change in volume of distribution. It was concluded that body weight is a significant covariant for the clearance and volume of distribution of bevacizumab in these species (24).

The pharmacokinetics of bevacizumab (0.1-10 mg/kg 90-min i.v. infusion on days 0, 28, 35 and 42) were examined in a phase I trial involving 25 patients with metastatic cancer who failed prior treatment. The pharmacokinetics of the agent appeared to be linear, with a half-life of approximately 21 days obtained at doses of 0.3 mg/kg or greater. Clearance was low (9.29 ml/kg/day at 0.1 mg/kg and 2.75-5.07 ml/kg/day at all other doses) and the volume of distribution was consistent with limited extravascular distribution (25).

A phase Ib trial involving 12 adult patients with advanced solid tumors examined the pharmacokinetics of bevacizumab (3 mg/kg i.v. infusions weekly for 8 weeks; the initial infusion was 90 min followed by a 60-min infusion and all subsequeent infusions were 30 min). Patients were also treated with either of the following: doxorubicin (50 mg/m^2 every 4 weeks), carboplatin (at AUC values of 6) plus paclitaxel (175 mg/m^2 every 4 weeks) or fluorouracil (5-FU; 500 mg/m^2) plus leucovorin (20 mg/m^2/week on weeks 1-6 every 8 weeks).The mean peak serum bevacizumab concentration obtained was 167 ± 46 μg/ml and the mean terminal half-life was 13 days (26).

The population pharmacokinetics of bevacizumab (0.1-10 mg/kg i.v. infusion over 4-24 weeks) as a single agent or in combination with other anticancer agents were reported following analysis of the above 2 clinical studies in addition to another phase I trial involving a total of 52 patients with advanced solid tumors. The pharmacokinetics of the agent were analyzed using a 2-compartment model with mixed modeling (NONMEM). The clearance, central volume of distribution, initial half-life and terminal half-life for a typical patient were 239 ml/day, 3260 ml, 1.85 days and 18.6 days, respectively. A 44 and 25% intersubject variability was obtained for clearance and volume of distribution values, respectively. Residual variability was 14%. Further analysis of results after dosing for up to 1 year revealed that like in cynomolgus monkeys, body weight was a significant covariant for the clearance and volume of distribution of bevacizumab. A 30% change in median body weight resulted in a 19% change in clearance and an 18% change in volume of distribution (24, 27).

A randomized phase II study involving 104 subjects with metastatic colorectal cancer examined the pharmacokinetics of bevacizumab (5 or 10 mg/kg every 2 weeks) alone or in combination with 5-FU/leucovorin (500 mg/m^2/week for 4/6 weeks). The disposition of bevacizumab was dose-linear. Mean clearance, volume of dis-

tribution and terminal half-life values from 62 patients receiving either 5 or 10 mg/kg bevacizumab were 2.79 ± 0.764 ml/kg/day, 45.7 ± 8.87 ml/kg and 12± 3.31 days, respectively Clearance was found to be about 15% higher in subjects with lower albumin. Eastern Cooperative Oncology Group (ECOG) status, sex, age or tumor burden did not influence the pharmacokinetics of bevacizumab (28).

A study analyzing the pharmacokinetic results of several randomized phase II studies involving patients with prostate, breast, non-small cell lung or colorectal cancers administered bevacizumab has demonstrated that the clearance of bevacizumab is highly related to time to disease progression and survival. Higher clearance values for bevacizumab were associated with a poorer prognosis. It was hypothesized that this relationship was due to the activation of the host's acute phase responses by a growing tumor. In fact, acute phase response markers (IL-6 , C-reactive protein) measured in patients with lung cancer were found to be strongly associated with clearance of bevacizumab, time to progression and survival (29).

Clinical Studies

To date, bevacizumab has undergone a number of phase I and II trials to examine the safety and efficacy of the agent in cancer patients. Results from a phase I, pharmacokinetic trial involving 25 patients with metastatic cancer who failed prior treatment showed that bevacizumab (0.1-10 mg/kg 90-min i.v. infusion on days 0, 28, 35 and 42) was well tolerated with no grade III or IV adverse events associated with the MAb. Grade I or II toxicities possibly related to treatment included asthenia, headache and nausea. Three episodes of tumor-related bleeding occurred during the treatment period. No clinically significant changes in biochemical, coagulation or hematologic parameters were observed with treatment and no impairments in wound healing were observed in those patients requiring surgical intervention; no patient developed antibodies to bevacizumab. No objective partial or complete responses were observed although a minor response (20-30% reduction in the sum of perpendicular diameters of pulmonary and lymph node metastases) was observed in a patient with renal cell carcinoma receiving 10 mg/kg bevacizumab. Of the 23 patients evaluable for response on day 70, 12 had stable disease while 11 had progressive disease (25). The results of this study and some of the other clinical studies that follow are summarized in Table I.

A phase Ib pilot study involving 12 adult patients with advanced solid tumors examined the long-term safety of bevacizumab (3 mg/kg i.v. infusion weekly for 8 weeks). Patients were also treated with either of the following: doxorubicin (50 mg/m^2 every 4 weeks), carboplatin (at AUC values of 6[AUC6]) plus paclitaxel (175 mg/m^2 every 4 weeks) or 5-FU (500 mg/m^2) plus leucovorin (20 mg/m^2/week on weeks 1-6 every 8 weeks). The median number of bevacizumab doses administered was 8. The grade III toxicities observed were probably not due to the MAb but to the chemotherapy component of treatment, and included 1 case of diarrhea in a patient also receiving 5-FU and thrombocytopenia in 2 patients on carboplatin plus paclitaxel. Results from pharmacological analysis of patients revealed an increase in total (free + bound) serum VEGF levels from day 0 (51 ± 39 pg/ml) to day 49 (211 ± 112 pg/ml). No patient developed antibodies to bevacizumab. Due to the small patient size, conclusions concerning the antitumor activity of the combination therapies could not be made. However, 3 patients (1 on each of the 3 treatment regimens) showed antitumor responses and were continued on treatment in an extension study for another 8 weeks (26).

Bevacizumab has also undergone phase II trials in patients with colorectal, hormone refractory prostate, advanced non-small cell lung and breast cancers.

A randomized, multicenter crossover trial involving 104 treatment naive patients with metastatic colorectal cancer receiving low- or high-dose (5 or 10 mg/kg every 2 weeks) bevacizumab in combination with 5-FU/leucovorin (500/500 mg/m^2 weekly for 6 cycles every 8 weeks) or 5-FU/leucovorin alone reported that bevacizumab was well tolerated. Any adverse events seen were related to 5-FU/leucovorin therapy. The preliminary results obtained also showed that bevacizumab in combination with 5-FU/leucovorin may increase response rates and prolong time to disease progression as compared to 5-FU/leucovorin alone. Objective response rates as determined in a blinded manner by an independent review facility were 42, 25 and 21% for the low- and high-dose bevacizumab + 5-FU/leucovorin groups and for the 5-FU/leucovorin group alone, respectively, and the time to disease progression was 9.2, 7.2 and 5.2 months, respectively (30). Retrospective analysis of the results of this trial revealed that survival may have been prolonged particularly in those patients with unfavorable prognostic indicators such as lower baseline albumin (increase in survival of +74% *vs.* +8%), older than 65 years (+58% *vs.* +22% in younger patients) and PS values greater than 0 (141% *vs.* 26% in patients with a PS of 0) (31).

The efficacy and safety of bevacizumab (10 mg/kg i.v. every 14 days for 6 infusions) as a single agent were examined in a phase II study involving 15 patients with hormone refractory prostate cancer. Of the 14 patients evaluable for response on day 70, none had an objective complete or partial response. Seven patients had progressive disease and 7 others had stable disease. Three possible mixed responses were observed. None of the 14 patients achieved a < 50% decrease in serum PSA, although 1 had a 25-50% decrease, 3 had a 0-25% decrease and 2 and 8 patients had a 14% and 25-50% increase in PSA, respectively. Although there were no significant changes in the McGill Present Pain Intensity Index, pain tended to increase throughout the study. The agent was generally well tolerated. Asthenia developed in 6 of the 15 patients and 2 patients developed severe hyponatremia that was thought to be unrelated to

Table I: Clinical studies of bevacizumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Metastasic cancer		Bevacizumab, 0.1 mg/kg i.v. over 90 min on days 0, 28, 35, 42 Bevacizumab, 0.3 mg/kg i.v. over 90 min on days 0, 28, 35, 42 Bevacizumab, 1 mg/kg i.v. over 90 min on days 0, 28, 35, 42 Bevacizumab, 3 mg/kg i.v. over 90 min on days 0, 28, 35, 42 Bevacizumab, 10 mg/kg i.v. over 90 min on days 0, 28, 35, 42	25	Although bevacizumab was safe and well tolerated, no evidence of activity was observed in this study	25
Cancer		Bevacizumab, 3 mg/kg i.v. over 30-90 min 1/wk x 8 wk + Doxorubicin, 50 mg/m^2 1x/4 wk (n=4) Bevacizumab, 3 mg/kg i.v. over 30-90 min 1/wk x 8 wk + Carboplatin, AUC=6 1x/4wk + Paclitaxel, 175 mg/m^2 1x/4 wk (n=4) Bevacizumab, 3 mg/kg i.v. over 30-90 min 1/wk x 8 wk + Fluorouracil, 500 mg/m^2 1/wk x 6 1x/8 wk + Leucovorin calcium, 20 mg/m^2 1/wk x 6 1x/8 wk (n=4)	12	Bevacizumab combined with chemotherapy was safe and may be effective in patients with advanced cancer	26
Colorectal cancer	Randomized	Bevacizumab, 5 mg/kg 1x/2 wk + Fluorouracil, 500 mg/m^2 1/wk x 6 1x/8 wk + Leucovorin calcium, 500 mg/m^2 1/wk x 6 1x/8 wk (n=35) Bevacizumab, 10 mg/kg 1x/2 wk + Fluorouracil, 500 mg/m^2 1/wk x 6 1x/8 wk + Leucovorin calcium, 500 mg/m^2 1/wk x 6 1x/8 wk (n=33) Fluorouracil, 500 mg/m^2 + Leucovorin calcium, 500 mg/m^2 1/wk x 6 1x/8 wk (n=36)	104	Bevacizumab combined with fluorouracil and leucovorin chemotherapy was well tolerated and may be effective in increasing response rates and prolonging time to disease progression in patients with metastatic colorectal cancer	28, 30
Breast, colorectal, non-small cell lung and prostate cancers	Randomized, pooled/meta-analysis	Bevacizumab Trastuzumab		Higher levels of bevacizumab and trastuzumab clearance were associated with a poorer prognosis in regard to time to disease progression and survival. Acute phase response markers such as IL-6 and C-reactive protein might be associated with the clearance of the drugs, as well as with time to disease progression and survival	29
Colorectal cancer	Randomized, multicenter	Bevacizumab + Fluorouracil + Leucovorin calcium Fluorouracil + Leucovorin calcium	99	Bevacizumab plus fluorouracil/ leucovorin chemotherapy may be effective in improving survival in patients with metastatic colorectal cancer, especially in those with an unfavorable prognosis	31
Prostate cancer	Open	Bevacizumab, 10 mg/kg i.v. infusion 1x/14 d x 12 wk	15	Bevacizumab was not effective in treating metastatic hormone refractory prostate cancer	32
Non-small cell lung cancer	Randomized, multicenter	Bevacizumab, 7.5 mg/kg 1x/3 wk + Carboplatin, AUC-6 + Paclitaxel, 200 mg/m^2 1x/3 wk x 6 cycles (n=32) Bevacizumab, 15 mg/kg 1x/3 wk + Carboplatin, AUC-6 + Paclitaxel, 200 mg/m^2 1x/3 wk x 6 cycles (n=35) Carboplatin, AUC-6 + Paclitaxel, 200 mg/m^2 1x/3 wk x 6 cycles (n=32)	99	The addition of bevacizumab (15 mg/kg) to carboplatin/paclitaxel chemotherapy increased time to disease progression and improved response rates in patients with advanced non-small cell lung cancer	33
Breast, non-small cell lung and prostate cancers	Open	Bevacizumab, 5-15 mg/kg 1x/2-3 wk x 14 [median] mo ± concomitant chemotherapy	28	Bevacizumab was well tolerated and might offer some benefit in patients with solid tumors in progression	39

treatment with the MAb. No serious bleeding events occurred. Response and toxicity data continue to be collected from the 3 patients with stable disease (32).

A multicenter randomized, crossover, phase II trial involving 99 patients with advanced stage IIIb (with pleural effusion)/IV or recurrent non-small cell lung carcinoma compared the efficacy and safety of low- and high-dose bevacizumab (7.5 and 15 mg/kg) in combination with carboplatin (AUC6)/paclitaxel (200 mg/m^2; C/P) given every 3 weeks for 6 cycles. A major concern of this study was that 6 bevacizumab-treated subjects developed sudden and life-threatening hemoptysis which was fatal in 4 patients. Further analysis of these patients comparing them to the 93 remaining patients involved in the study and 24 matched controls revealed that squamous cell histology was the most likely risk factor for pulmonary hemorrhage; 67% (4/6) of the bevacizumab-treated patients who suffered from hemoptysis had squamous cell histology as compared to only 20% (20/99) of the entire study population. Moreover, 5 of the 6 subjects who experienced hemoptysis had centrally located lesions adjacent to pulmonary arteries or veins and 3 and 4 of the 6 patients had either cavitation or necrosis at baseline or on therapy, respectively. Results obtained from the trial, which were analyzed in a blinded manner by an independent review facility, suggest that 15 mg/kg bevacizumab in combination with C/P may increase objective response rates (34.3% *vs.* 25 and 21.9% for C/P alone and low-dose bevacizumab + C/P, respectively) and prolong the time to disease progression (207 days *vs.* 181 and 124 days, respectively) as compared to C/P therapy alone and low-dose bevacizumab + C/P. Further analysis of these patients showed that treatment with bevacizumab significantly increased survival of patients. However, the agent had no significant effect on the clinical course of malignant pleural effusions. Thus, it was concluded that malignant pleural effusions associated with non-small cell lung cancers should be treated with conventional therapies (33-36).

The tolerability and efficacy of bevacizumab as a single agent (3 or 10 mg/kg i.v. infusion every 2 weeks until disease progression or for a maximum of 13 infusions) was shown in a study involving 35 patients with metastatic breast cancer who had progressed following at least one anthracycline or taxane-based treatment regimen. Treatment was well tolerated and no fatal adverse events associated with treatment occurred. One patient discontinued due to development of malignant hypertension and nephrotic syndrome after starting bevacizumab treatment and another patient experienced a severe case of hypertension. Of those patients receiving 3 mg/kg, 1 patient had a partial response with shrinkage of a cervical lymph node. Of those patients treated with 10 mg/kg, 1 patient had a complete response with shrinkage of a supraclavicular lymph node, 1 patient with skin/subcutaneous disease had a partial response and 2 patients with skin/subcutaneous disease showed regression of skin/subcutaneous nodules. There are 3 patients continuing on 10 mg/kg bevacizumab and a third cohort has been enrolled to receive the 10 mg/kg dose (37).

The efficacy and tolerability of bevacizumab (3, 10 or 20 mg/kg i.v. infusion every 2 weeks until disease progression) was further shown in a phase II dose-escalation study involving 75 women with previously treated (median of 2 prior chemotherapy regimens) metastatic breast cancer. The median duration of treatment was 10 weeks. The dose-limiting toxicity was headache (1 case each of grade III and IV) associated with nausea and vomiting seen in 4 patients treated with the 20 mg/kg dose. There were 4 discontinuations which were due to hypertensive encephalopathy and nephrotic syndrome at 3 mg/kg, proteinuria at 10 mg/kg, nephrotic syndrome at 20 mg/kg and severe headache, nausea and vomiting at 20 mg/kg. Objective responses were seen in 7 of the 75 patients, of which 1 was a compete response in a supraclavicular node in a patient receiving 10 mg/kg which recurred 3 months after completion of 1 year of therapy. Six patients with disease in lymph nodes, skin, pleura, bone and liver had partial responses (4 were confirmed); the median duration of confirmed responses was 5.6 months. It was noted that responders had a smaller tumor burden, lower ECOG status and higher albumin at baseline as compared to the entire study population. Ongoing responses or stable disease were seen in 12 of the 75 patients at tumor assessment at 5 months. Three patients have been treated for 1 year or more without disease progression. The median survival was 10.2 months (38).

Data from an ongoing extension study involving a total of 52 patients with advanced solid tumors (colorectal, non-small cell lung, breast, prostate) who had completed 6-12 previous months of bevacizumab therapy in phase I/II trials showed that some patients who progress after 6-12 months may benefit from retreatment with the agent (5-15 mg/kg every 2-3 weeks). Results were presented from 28 patients, of whom 18 received concomitant chemotherapy. Of these patients who had been treated previously for 1 year and observed in an observation period of therapy for 6 months or less, 16 have restarted bevacizumab therapy at progression. Long-term treatment with the agent was generally well tolerated. Significant adverse events observed after restarting therapy were 5 cases of deep venous thrombosis. Other adverse events included grade 2/3 hypertension in 3 patients, grade 1 proteinuria in 1 patient and grade 2 and 4 gastrointestinal bleeds in 2 patients with colorectal cancer, respectively. So far, during the first course, 1 and 8 complete and partial responses, respectively, have been observed. Seven patients had stable disease and none had disease progression. The median time to disease progression was 13.2 months. During the second course, 2 partial responses and 8 stable diseases were observed and the median time to disease progression was 7.9 months; 6 patients had progressive disease during this course. Median survival (range 17 to 40+ months) has not yet been reached, although 20 patients are still alive (39).

Bevacizumab continues to undergo phase II and III trials for colorectal cancer and phase III trials for breast

cancer. Enrollment has been completed for a phase III trial which will examine the efficacy of bevacizumab in combination with capecitabine as compared to capecitabine alone as a treatment for 400 patients with refractory metastatic breast cancer. Enrollment has also been completed for a study involving 900 patients with metastatic colorectal cancer where bevacizumab will be combined with CPT-11/5-FU/leucovorin and compared to treatment with CPT-11/5-FU/leucovorin alone or a combination of bevacizumab and 5-FU/leucovorin. Bevacizumab (Avastin™) in combination with capecitabine has received fast-track approval status from the FDA for treatment of metastatic breast cancer (40).

Source

Genentech, Inc. (US).

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