A Review on Bevacizumab: An Anti-Cancer Drug

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Review Article

ABSTRACT

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Cancer is one of the most wide spread diseases. Now-a-days, due to the advanced technologies drug for different kinds of cancer are available in the market. Bevacizumab (Avastin) is a one of the well-known anti-cancer drug which is used for different kinds of cancer. Bevacizumab (Avastin) interferes with growth of the cancerous cells. It is a humanized monoclonal antibody drug which blocks angiogenesis by inhibiting Vascular Endothelial Growth Factor A (VEGF-A). Researchers have shown the advantages of this drug in metastatic breast cancer, in blindness, ovarian cancer and many more. Before using this drug, patient should consult to the doctor and should be aware of its side effects in the future.

INTRODUCTION

Bevacizumab categorized as a "monoclonal antibody" and "anti-angiogenesis" drug that inhibits the development of new blood vessels (angiogenesis) ^[1-5]. Some angiogenesis inhibitors are endogenous and others are acquired exogenously through pharmaceutical drugs or food plan ^[6-10]. Bevacizumab blocks angiogenesis with the aid of inhibiting Vascular Endothelial Growth Factor A (VEGF-A). VEGF-A is a signaling protein which is responsible for the growth of new blood vessels. Mostly, this protein will supply blood to those cells and tissues which are deprived of oxygenated blood due to compromised blood circulation. VEGF-A plays a major role in rheumatoid arthritis, diabetic retinopathy, breast cancer ^[11-14].

Few problems have also been identified with VEGF-A. Overexpression of VEGF-A is responsible for the development of many diseases. For example, those tumors which can express VEGF-A can continue growing beyond their size limit because of VEGF-A property that they can develop this enhanced blood supply that is angiogenesis. Bevacizumab used to be the first clinically on hand angiogenesis inhibitor in the US. This medication is an artificial antibody (IgG1) used to treat kidney, cervical, ovarian, colon, and rectal melanoma ^[15-20]. Bevacizumab can be used to treat lung melanoma (non-small cell sort), detailed forms of brain tumors, and melanoma observed within the fallopian tube or lining of the belly wall (peritoneal) ^[21-24]. It was firstly permitted by the food and Drug Administration (FDA) as a remedy for different forms of cancer. Its use to treat eye disorder is viewed as an "offlabel" use ^[25-30]. On 14th November, 2014 FDA permits the use of medicines for the treatment of cancer ^[31-35].

MEDICAL USES OF BEVACIZUMAB

- Bevacizumab can be used in combination with chemotherapy routine in fallopian tube and primary peritoneal cancer. FDA approved the intravenous infusion of the solution of this drug with other drug like paclitaxel, topotecan.
- Cure for non-squamous, non-small lung melanoma along with the combination of carboplatin/paclitaxel chemotherapy. The approval of taking this drug is solely depends upon the study which had done. Study showed a 2 month improvement in overall survival in patients who are treated with Bevacizumab ^{[36-41].}
- Remedy of metastatic breast melanoma used as part of a blend chemotherapy regimen.
- Healing of glioblastoma (GBM).
- Bevacizumab was once approved by the FDA in February 2004 for use in metastatic colorectal cancer when used with common chemotherapy treatment (as first-line cure) and with 5-fluorouracil-based healing for 2nd-line metastatic colorectal cancer. Bevacizumab has additionally been examined as an add on to

other chemotherapy medications in men and women with non-metastatic colon cancer undergoing surgical removing ^[42-46]. It was authorized for use in colorectal cancer in 2005.

- Bevacizumab has recently been utilized by ophthalmologists in an off-label use as an intravitreal agent within the therapy of proliferative (neovascular) eye illnesses, mainly for choroidal neovascular membrane (CNV) ^[47-52]. Despite the fact that not currently authorized through the FDA for such use, the injection of 1.25-2.5 mg of bevacizumab into the vitreous cavity has been carried out without enormous intraocular toxicity ^[53-57]. Many retina professionals have noted spectacular outcome in the atmosphere of CNV, proliferative diabetic retinopathy, neovascular glaucoma, and diabetic macular oedema, retinopathy of prematurity and macular oedema secondary to retinal vein occlusions ^[58-63].
- Avastin is given directly into the bloodstream that is intravenously. The principal measurement is given
 more than an hour and a half ^[64-69]. The first dose of bevacizumab is given over 90 minutes. The measure
 of Bevacizumab depends upon physical make-up which will relies upon numerous clarifications, including
 pinnacle and weight, regular prosperity or diverse medical issues and the kind of melanoma or
 circumstance being managed. Human services supplier will check concerning the measurement ^[70-75].

SIDE EFFECTS

- Results are usually predictable in terms of their onset and duration.
- Side effects can go away after the treatment i.e. results can be reversible. There is no relationship between the presence or severity of side effects and the effectiveness of the treatment ^[76-81].
- There is not any knowledge as to the frequency of adverse reactions that could be attributed to Bevacizumab alone. (In clinical stories Bevacizumab used to be utilized in combination with other chemotherapy medicines).
- The following effects are common (occurring in greater than 30%) for patients taking Bevacizumab.
- Generalized weak spot, soreness, stomach affliction, Nausea & vomiting, negative appetite, Constipation, upper respiratory illness, low white blood cell depend (this will put patient at accelerated threat for contamination), Proteinuria, nose bleed, numbness, diarrheal, hair loss, mouth sores, loss of fertility, watery eyes, headache ^[82-85].
- Rare side effects are: Reversible Posterior Leucoencephalopathy Syndrome (RPLS) following these symptoms headaches, seizures, confusion, eye sight problems, excessive sleep, change in behavior, chances of getting high blood pressure.
- Osteonecrosis that is damage to the teeth and jawbone.
- Chances of having severe bleeding (hemorrhage).
- Nephrotic syndrome: condition which is recognized by high levels of protein in the urine, low level of protein in the blood, swelling around the eyes especially ^[86-90].
- Patients who have received radiation therapy to the chest wall are at the risk of getting congestive heart failure.
- Some delayed effects are also related to the Bevacizumab therapy for example disruption in normal menstrual cycle and can also cause infertility.
- Bevacizumab may cause a hole in the wall of stomach or intestine which can be a life threatening condition. Consult to the doctor immediately if suffering from stomach pain, fever, constipation.
- Sometimes because of this therapy there may be chances of having delay in the wound healing such as some cuts made by doctor during the surgery. Wounds which are closed may have chance of open up again.

PRECAUTION

- Before beginning Bevacizumab treatment, patient should inform the health practitioner about different remedy as he/she is having (including prescription, over-the-counter, nutrition, herbal cures, etc.).
- Do not receive any kind of immunization or vaccination without medical professional's approval even as taking Bevacizumab.

- Inform health practitioner if you're pregnant or could also be pregnant previous to opening this medication. Pregnancy category C (use of Bevacizumab during being pregnant can be dangerous to the fetus). Information has shown that Bevacizumab may damage your unborn child. Taking Bevacizumab could cause a girl's ovaries to discontinue working and could impair her capacity to have children ^[91-95].
- For both men and women: do not conceive a child (get pregnant) whilst taking Bevacizumab. Barrier methods of contraception, reminiscent of condoms, are advocated. Consult with your healthcare professional when to get pregnant or conceive a baby after remedy/treatment only.
- Don't breastfeed during uptake of Bevacizumab.
- Consult to the health care professional first before undergoing any surgical procedure. Bevacizumab must no longer be used for 28 days before or after surgery and until surgical wounds are utterly healed ^[96-100].
- Patient should also know about the self-care tips for example:
- Maintain good nutrition and get plenty of rest.
- Avoid sun as long as you can, or else wear sun screen.
- Drink plenty of water at least two or three quarts of fluid every 24 hours.
- Try not to drink any alcoholic beverages.
- To avoid mouth sores, keep good hygiene of mouth. If possible use baking soda and rinse with it thrice in a day.

REFERENCES

- 1. Bahri S, et al. Initial experience of monitoring response of breast cancer to bevacizumab-containing chemotherapy using a new integrin specific PET imaging tracer [F-18]RGD-K5. J Mol Imaging Dynam. 2015;5:116.
- 2. Chikazawa K, et al. Bevacizumab treatment for recurrent ovarian cancer with isolated metastasis to the lymph node. Gynecol Obstet. 2015;5:329.
- 3. Baba Y, et al. The role of bevacizumab in the management of head and neck squamous cell carcinoma patients. Chemotherapy. 2015;4:163.
- 4. Tabouret E, et al. Bevacizumab trough concentration in recurrent glioblastoma patients. J Integr Oncol. 2015;4:138.
- 5. Chen J, et al. Recurrent invasive pulmonary mucinous adenocarcinoma showing responses to platinumbased chemotherapy regimens with docetaxel and bevacizumab: a case report. Chemotherapy. 2014;4:151.
- Telbizova-Radovanova K, et al. Optical coherence tomography patterns in diabetic macular edema can predict the effectiveness of intravitreal bevacizumab combined with macular photocoagulation. J Clin Exp Ophthalmol. 2014;5:355.
- 7. Pistelli M, et al. Paclitaxel and bevacizumab in first line-treatment patients with HER-2 negative advanced breast cancer: who could benefit? Chemotherapy. 2014;3:127.
- 8. Rottenberg Y, et al. Bevacizumab in colorectal cancer: toxicity epidemiology, management and correlation with response. J Gastrointest Dig Syst. 2013;3:128.
- 9. Zhang B, et al. A potential administration-time dependent effect of bevacizumab in improving overall survival and increasing metastasis in metastatic colorectal cancer. Chemotherapy. 2013;2:108.
- 10. Koh H, et al. A rare case of persistent pneumothorax in non-small cell lung cancer on bevacizumab therapy. J Pulm Respir Med. 2013;S14:001.
- 11. Alhammami H, et al. Subconjunctival bevacizumab injection in treatment of recurrent pterygium. J Clin Exp Ophthalmol. 2013;4:267.
- 12. Sudhalkar A, et al. Outcomes of post-operative topical bevacizumab in primary pterygium surgery: a case series. J Clin Exp Ophthalmol. 2012;3:243.
- 13. Yoon KC, et al. Is combined photodynamic therapy and subconjunctival bevacizumab injection useful for corneal neovascularization? J Clin Exp Ophthalmol. 2011;2:106e.
- 14. Ghanem AA, et al. Trabeculectomy with or without intraoperative sub-conjunctival injection of bevacizumab in treating refractory glaucoma. J Clin Exp Ophthalmol. 2011;2:131.

- 15. Salman AG, et al. Intravitreal bevacizumab injection as a primary therapy for threshold disease (ROP) in al qassim region. J Clin Exp Ophthalmol. 2010;1:113.
- 16. Paula JS, et al. Long-term intraocular pressure control in a case of neovascular glaucoma treated with repeated intravitreal bevacizumab injections. J Clin Exp Ophthalmol. 2011;2:170.
- 17. Sayanagi K, et al. Transient choroidal thinning after intravitreal bevacizumab injection for myopic choroidal neovascularization. J Clin Exp Ophthalmol. 2011;2:165.
- 18. Garde-Noguera J, et al. Lactate dehydrogenase-5 (Ldh-5) immunohistochemical expression as predictor of efficacy of first-line therapy in patients with advanced colorectal cancer treated with chemotherapy and bevacizumab. J Clin Exp Pathol. 2016;6:293.
- 19. Matrana MR, et al. A case of metastatic papillary renal cell carcinoma responsive to bevacizumab and erlotinib. Med Surg Urol. 2016;5:166.
- 20. Osman U, et al. Bronchial necrosis following bevacizumab and stereotactic body radiotherapy for treatment of metastatic breast cancer. J Pulm Respir Med. 2016;6:345.
- 21. Salutari V, et al. Commentary on bevacizumab in ovarian cancer: focus on clinical data and future perspectives trends. Gynecol Oncol. 2016;1:103.
- 22. Heissner K, et al. Treatment associated interstitial pulmonary toxicity of temozolomide plus bevacizumab for locally advanced solitary fibrous tumor. J Pulm Respir Med. 2016;6:314.
- 23. Abd A, et al. Therapeutic effects of extracts from spirulina platensis versus bevacizumab on inflammationassociated corneal neovascularization. J Med Surg Pathol. 2015;1:102.
- 24. Ohnaru K, et al. Atypical femoral fracture in a patient with metastatic breast cancer during denosumab therapy. J Clin Case Rep. 2016;6:737.
- 25. El-Lathy HA, et al. The impact of pretreatment 18F-FDG (PET/CT) maximum standardized uptake value and neutrophil/lymphocyte ratio (NLR) in predicting prognosis in surgically treated oligometastatic breast cancer patients. J Nucl Med Radiat Ther. 2016;7:271.
- 26. El-Lathy HA, et al. The prognostic role of pretreatment 18F-FDG (PET/CT) maximum standardized uptake value in multiple or oligometastatic breast cancer patients. J Nucl Med Radiat Ther. 2015;6:236.
- 27. Reure J, et al. Her2 positive metastatic breast cancer patient without any sign of recurrence 5 years after cessation of trastuzumab: a case report. Clin Pharmacol Biopharm. 2015;4:136.
- 28. Andrea CG, et al. Complete response in patient with metastatic breast cancer treated with metronomic chemotherapy. J Blood Lymph. 2015;5:136.
- 29. Ahmad A, et al. Nanosomal paclitaxel lipid suspension demonstrates higher response rates compared to paclitaxel in patients with metastatic breast cancer. J Cancer Sci Ther. 2015;7:116-120.
- 30. Espinal E, et al. Pitfalls on screening in clinical trials: positive pregnancy test in a nonpregnant woman with metastatic breast cancer. J Clin Trials. 2014;4:187.
- 31. Oh B, et al. Effects of qigong on quality of life, fatigue, stress, neuropathy, and sexual function in women with metastatic breast cancer: a feasibility study. Int J Phys Med Rehabil. 2014;2:217.
- 32. Banhegyi RJ, et al. The role of fulvestrant in the treatment of metastatic breast cancer: a case report. J Steroids Horm Sci. 2013;5:131.
- 33. Sakamoto Y, et al. Bilateral typical femoral fractures in a patient with metastatic breast cancer on long-term bisphosphonate therapy: a case report. J Osteopor Phys Act. 2014;2:110.
- 34. Brancikova D, et al. Bone markers in the treatment of cancer related bone disease in patients with metastatic breast cancer. J Cancer Sci Ther. 2014;6:027-031.
- 35. Cody JJ, et al. Improving oncolytic herpes simplex virus for metastatic breast cancer. J Genet Syndr Gene Ther. 2013;4:126.
- 36. Bostanabad SZ, et al. Isolation of mycobacterium chelonae in the sputum and cervical lymph nodes of patient with metastatic breast cancer. Mycobact Dis. 2012;2:106.
- Copur MS, et al. Letrozole and fulvestrant combination in second line or more for estrogen receptor positive metastatic breast cancer; efficacy and predictive factors of response. J Cancer Sci Ther. 2011;S2-003.
- 38. Wong MHY, et al. Metastatic breast cancer mimicking ocular myaesthenia gravis. J Clin Exp Ophthalmol. 2011;2:179.
- 39. Mori R, et al. Effective hormone therapy reduces the efficacy of subsequent chemotherapy in hormonereceptor-positive metastatic breast cancer. Chemotherapy. 2016;5:210.

- 40. Hassanen EM, et al. Comparative study between vinorelbine based versus taxanes based chemotherapy in treatment of parenchymal metastatic breast cancer. Chemotherapy. 2016;5:208.
- 41. Hara F, et al. Randomized, optimal dose finding, phase li study of tri-weekly nabpaclitaxel in patients with metastatic breast cancer. J Clin Trials. 2016;6:267.
- 42. Rashid OM, et al. A systematic approach to preclinical trials in metastatic breast cancer. Chemotherapy. 2016;5:204.
- 43. Taira N, et al. Cohort study of secondary endocrine therapy in metastatic breast cancer with a poor response to initial endocrine therapy. J Clin Trials. 2016;6:260.
- 44. Maloney JP, et al. Platelet vascular endothelial growth factor is a potential mediator of transfusion-related acute lung injury. J Pulm Respir. Med. 2014;4:212.
- 45. Tagawa S, et al. Surface-bound vascular endothelial growth factor promotes prolonged activation of endothelial cells: a new technology for capturing endothelial progenitor cells by intravascular stents. J Tissue Sci Eng. 2014;5:140.
- 46. Berezin AE, et al. Predictive value of circulating vascular endothelial growth factor-1 in arterial hypertension patients. Intern Med. 2013;S11:006.
- 47. Berezin AE, et al. Predictive value of circulating vascular endothelial growth factor-1 level measured repeatedly during long-term follow-up in patients with arterial hypertension after acute ischemic stroke. Angiol. 2014;2:119.
- 48. Garcia EA, et al. Pro and anti-angiogenic vascular endothelial growth factors expression in benign and malignant thyroid lesions. Thyroid Disorders Ther. 2013;2:123.
- 49. Kumar MA, et al. Prospective role of indian medicinal plants in inhibiting Vascular Endothelial Growth Factor (VEGF) mediated pathological angiogenesis. J Homeop Ayurv Med. 2013;2:121.
- 50. Ahmad A, et al. Prognostic effect of vascular endothelial growth factor 936C/T polymorphisms on tumor growth pattern and survival in patients diagnosed with colon carcinoma. J Tumor Res. 2016;2:1.
- 51. Obi N, et al. Human umbilical vein endothelial cells migration in matrigel by the concentration gradient of vascular endothelial growth factor. J Biotechnol Biomater. 2015;5:210.
- 52. Medvedkova SA, et al. Vascular endothelial growth factor-1 level and functional neurologic recovery after ischemic hemispheric stroke. Neurochem Neuropharm. 2015;1:102.
- 53. Kianersi F, et al. Anti-vascular endothelial growth factor for choroidal neovascularization associated with toxoplasmosis: a case series. J Clin Exp Ophthalmol. 2015;6:463.
- 54. Ahmed M, et al. Vascular Endothelial Growth Factor Inhibitors: Blocking Angiogenesis and Improving Outcomes. Clon Transgen. 2015;4:e116.
- 55. Seki Y, et al. Landiolol hydrochloride normalizes diminished levels of cardiac Vascular Endothelial Growth Factor (VEGF) signaling system components in lipopolysaccharide-induced sepsis independent of inflammatory markers. J Vasc Med Surg. 2015;3:193.
- 56. Cobleigh MA, et al. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol. 2003;30:117-124.
- 57. Cohen MH, et al. FDA drug approval summary: Bevacizumab plus FOLFOX4 as second-line treatment of colorectal cancer. Oncologist. 2007;12:356-361.
- 58. Cohen MH, et al. FDA drug approval summary: Bevacizumab (avastin) plus carboplatin and paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. Oncologist. 2007;12:713-718.
- 59. Carmeliet P. Angiogenesis in life, disease and medicine. Nature. 2005;438:932-936.
- 60. Ferrara N. VEGF and the quest for tumour angiogenesis factors. Nat Rev Cancer. 2002;2:795-780.
- 61. Folkman J. Tumor angiogenesis: Therapeutic implications. N Engl J Med. 1971;285:1182-1186.
- 62. Korpanty G, et al. Molecular and clinical aspects of targeting the VEGF pathway in tumors. J Oncol. 2010;2010:652320.
- 63. Yancopoulos GD, et al. Vascular-specific growth factors and blood vessel formation. Nature. 2000;407:242-248.
- 64. Leung DW, et al. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science. 1989;246:1306-1309.
- 65. Ferrara N, et al. The biology of VEGF and its receptors. Nat Med. 2003;9:669-676.

- 66. Holmes K, et al. Vascular endothelial growth factor receptor-2: Structure, function, intracellular signaling and therapeutic inhibition. Cell Signal. 2007;19:2003-2012.
- 67. Ferrara N. Vascular endothelial growth factor: Basic science and clinical progress. Endocr Rev. 2004;25:581-611.
- 68. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy. Nat Med. 2001;7:987-989.
- 69. Jain RK. Normalization of tumor vasculature: An emerging concept in antiangiogenic therapy. Science. 2005;307:58-62.
- 70. Duda DG, et al. Antiangiogenics: The potential role of integrating this novel treatment modality with chemoradiation for solid cancers. J Clin Oncol. 2007;25:4033-4042.
- 71. Palmer AM, et al. Society for Medicines Research: 40th anniversary symposium. Drug News Perspect. 2007;20:191-196.
- 72. Ferrara N. Anti-angiogenic drugs to treat human disease: an interview with Napoleone Ferrara by Kristin H. Kain. Dis Model Mech. 2009;2:324-325.
- 73. Ribatti D. Napoleone Ferrara and the saga of vascular endothelial growth factor. Endothelium. 2008;15:1-8.
- 74. Ferrara N. From the discovery of vascular endothelial growth factor to the introduction of avastin in clinical trials an interview with Napoleone Ferrara by Domenico Ribatti. Int J Dev Biol. 2011;55:383-388.
- 75. Giantonio BJ, et al. Bevacizumab in combination with FOLFOX4 for previously treated metastatic colorectal cancer: results from ECOG E3200. J Clin Oncol. 2007;25:1539-1544.
- 76. Kabbinavar FF, et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol. 2005;23:3706-3712.
- 77. Kabbinavar FF, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first line metastatic colorectal cancer: results of randomized phase II trial. J Clin Oncol. 2005;23:3697-3705.
- 78. Kabbinavar F, et al. Phase II randomized trial comparing bevacizumab plus fluorouracil(FU)/leucovorin(LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol. 2003;21:60-65.
- 79. Saltz LB, et al. Bevacizumab in combination with oxaliplatin based chemotherapy as first line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26:2013-2019.
- 80. Hurwitz H, et al. Bevacizumab plus irinotecan, flouorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335-2342.
- 81. Brufsky A. Angiogenesis inhibition and metastatic breast cancer: cases and answers. 2010.
- 82. Kerbel RS. Tumor angiogenesis. N Engl J Med. 2008;358:2039-2049.
- 83. Mayer and Robert J. Two Steps Forward in the Treatment of Colorectal Cancer. N Engl J Med. 2004;350:2406-2408.
- 84. Linderholm B, et al. Correlation of vascular endothelial growth factor content with recurrences, survival, and first relapse site in primary node-positive breast carcinoma after adjuvant treatment. J Clin Oncol. 2000;18:1423-1431.
- 85. Weidner N, et al. Tumor angiogenesis: a new significant and independent prognostic indicator in early stage breast carcinoma. J Natl Cancer Inst. 1992;84:1875-1887.
- 86. Tufail A, et al. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. BMJ. 2010;340:c2459.
- 87. Rosen LS, et al. Targeting signal transduction pathways in metastatic breast cancer a comprehensive review. Oncologist. 2010;15:216-235.
- 88. Griffioen AW and Molema G. Angiogenesis: potentials for pharmacologic intervention in the treatment of cancer, cardiovascular diseases, and chronic inflammation. Pharmacol Rev. 2000;52:237-68.
- 89. Ferrara N and Davis-Smyth T. The biology of vascular endothelial growth factor. Endocr Rev. 1997;18:4-25.
- 90. Lordick F, et al. Increased risk of ischemic bowel complications during treatment with bevacizumab after pelvic irradiation: report of three cases. Int J Radiat Oncol Biol Phys. 2006;64:1295-1298.
- 91. Griffin RJ, et al. Angiogenesis treatment, new concepts on the horizon. Angiogenesis. 2006;9:67-72.
- 92. Willett CG, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med. 2004;10:145-147.
- 93. Miller KD, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 2005;23:792-799.

- 94. Kerbel RS, et al. Possible mechanisms of acquired resistance to anti-angiogenic drugs: implications for the use of combination therapy approaches. Cancer Metastasis Rev. 2001;20:79-86.
- 95. Hanna NN, et al. Antitumor interaction of short-course endostatin and ionizing radiation. Cancer J. 2000;6:287-293.
- 96. Gorski DH, et al. Potentiation of the antitumor effect of ionizing radiation by brief concomitant exposures to angiostatin. Cancer Res. 1998;58:5686-5689.
- 97. Mauceri HJ, et al. Combined effects of angiostatin and ionizing radiation in antitumour therapy. Nature. 1998;394:287-291.
- 98. Eskens FA and Sleijfer S. The use of Bevacizumab in colorectal, lung, breast, renal and ovarian cancer. Where does it fit? Eur J Cancer. 2008;33:2350-2356.
- 99. Fuchs CS, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol. 2007;25:4779-4786.
- 100. Guan ZZ, et al. Efficacy and safety of bevacizumab plus chemotherapy in Chinese patients with metastatic colorectal cancer: a randomized phase III ARTIST trial. Chin J Cancer. 2011;30:682-689.