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Research Article

CONCISE REVIEW ON ANTICANCER DRUG BEVACIZUMAB FOR DEVELOPING A NEW MARKETING STRATEGY IN INDIA

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ABSTRACT

As increased angiogenesis has been related with the progression of Ovarian cancer, Metastatic colorectal cancer (mCRC), Metastatic renal cell, Glioblastoma multiforme, Non squamous non-small cell lung cancer (NSCLC), number of anti-angiogenic agents have been investigated or are currently in development, as a potential treatment options for patients with advanced disease. Bevacizumab, a recombinant monoclonal antibody having targeted action against vascular endothelial growth factor (VEGF) has gained European Medical Agency (EMA) approval for treating the cancer mentioned above in combination with chemotherapeutic agents. Globally the incidence/new cases for the cancer is about 14.1 millions, 8.2 million cancer deaths and about five year prevalence was around 32.6 million cancers individuals that were above 15 years. Globocan 2012 indicates that the number might increase to 19.3 million new cancer cases by 2025. In India there are about 1.1 million new cancer cases, 682,830 cancer deaths and five-year prevalence was around 1.8 million individuals having or diagnosed with cancer. There are very few targeted therapies that are available for treating such type of cancer and Avastin is one of innovator product are available to patients. But due to its high cost it become difficult for patients use the drug for treatment purpose. So there arises a need to bring a quality generic version of the innovator drug to benefit Indian patients. Many leading Indian companies are striving to develop or manufacture such lifesaving drugs to make it available to Indian patients. A systemic literature survey was carried out to identify data available for in such type of cancer and to foster the strategy with a vision to bring global availability of the quality product to Indian patients.

Keywords: Angiogenesis, Monoclonal antibody, Bevacizumab, Targeted action, ovarian cancer, Metastatic colorectal cancer, vascular endothelial growth factor.

1. INTRODUCTION

Bevacizumab (Avastin; Genentech) is a humanized anti-VEGF (vascular endothelial growth factor) monoclonal IgG1 antibody (molecular weight, 149 kDa). In combination with chemotherapy, it is being approved for the treatment of advanced colorectal cancer (CRC), advanced non-small cell lung cancer (NSCLC), metastatic breast cancer (MBC) and advanced renal cell cancer. Vascular endothelial growth factor A (VEGF) is the potent pro-angiogenic growth factor that is responsible for angiogenesis and stimulates the proliferation, migration/transfer, and survival of endothelial cells. As one of the more vital proteins also expressed by tumor cells, VEGF is a vital target of anticancer therapy. Circulating VEGF binds to VEGF receptor (VEGFR)-1 and VEGFR-2 and to its co-receptors neuropilin (NRP)-1 and NRP-2 having a high binding affinity. These are the receptors that are expressed on the surface of endothelial cells, and they play an important role in the development of angiogenesis by stimulating the migration and proliferation of endothelial cells. Bevacizumab acts by selectively binding to circulating VEGF, and thus inhibiting the binding of VEGF to its cell surface receptors. This inhibition leads to a reduction or decreases in microvascular growth of tumor blood vessels and thus limits the blood supply to tumor tissues. These effects also lower or decreases tissue interstitial pressure and increase vascular permeability, which may increase delivery of chemotherapeutic agents, and favor apoptosis of tumor endothelial cells[1]. Bevacizumab improves progression-free survival (PFS) in these cancers; it is not effective for all patients. Predictive markers/indicators of Bevacizumab efficacy have been assessed in many clinical trials, however, no validated biomarker is available to predict Bevacizumab efficacy and identify the patients who could benefit from Bevacizumab[2]. Angiogenesis represents a significant step in the pathogenesis, invasion, progression and growth of metastatic phenotype of various types of cancer and is regulated by pro-angiogenic factors such as vascular endothelial growth factor (VEGF). High expression levels of VEGF are associated with a poor prognosis and reduced survival in patients with cancer. In this context, the theoretical block of tumor angiogenesis is identified by monoclonal antibodies to factor soluble serum VEGF to its receptor or VEGFR (in different isoforms) or small molecules directed to the tyrosine-kinase receptor that appears to be a valid basis for setting effective therapies[3].

2. INVESTIGATIONAL COMBINATION THERAPIES

2.1 In Metastatic Colorectal Cancer

Colorectal cancer is the third most diagnosed cancer in men and the second in women worldwide, with an estimation of over 1.2 million new cases and 608,700 deaths in 2008. In an attempt for controlling the disease, targeted therapy has been a matter of wide research. Anti-angiogenesis is one of the vital theories involved in this approach. One of the key pathways related with the anti-angiogenic process is the vascular endothelial growth factor (VEGF) family, with increased expression of its receptors observed not only in colorectal neoplasms, but in a wide variety of different tumors. This circumstance led to the development of many VEGF inhibitors, amongst which Bevacizumab is one of the most common[4]. Bevacizumab in colorectal cancer was studied initially in the metastatic setting, and it was approved by US Food And Drug Administration (FDA) in 2004, based on a survival benefit found in the AVF2107 trial with the Saltz' irinotecan, 5-fluorouracil and leucovorin (IFL) regimen comparing bolus irinotecan, 5 fluorouracil, leucovorin (IFL), and placebo therapy with IFL and Bevacizumab have showed 4.7 month and 4.4 month increase in median OS and PFS, respectively. However, FOLFOX, FOLFIRI and XELOX became standard first-line therapy for mCRC now. Comparing FOLFOX regimen, IFL showed more early deaths, higher toxicity, and poorer effectiveness in N9741 study[5].

The first study aims to evaluate this combination, AVF2107, enrolled 813 patients in a double-blind, randomized phase III study involving IFL regimen, and revealed a clear advantage on OS (4.7 months) as well as PFS with the addition of Bevacizumab at 5 mg/kg.

Table 1: Trial Characteristics

Study characteristics		Bevacizumab schedule	Regimens	Median OS	Median PFS
Irinotecan-based therapy	Hurwitz, 2004 (AVF2107)	5mg/kg every 14 d	Irinotecan, 5-Fluorouracil and Leucovorin (IFL/FOLFIRI)	20.3 months	10.6 months
	Stathopoulos, 2010	7.5 mg/kg every 21 d	Irino 135 mg/m2 + 5 FU 500 mg/m2 + LV 200 mg/m2 every 21 d	Not reported	Not reported
Oxaliplatin-based therapy	Saltz, 2008 (NO16966)	7.5 mg/kg every 21 d (XELOX) or 5 mg/kg every 14 d (FOLFOX4)	XELOX or FOLFOX4	Not reported	Not reported
Fluorouracil alone	Kabinnavar, 2003	10 mg/kg every 14 d (32 patients). 5 mg/kg every 14d (33 patients).	5FU + L + BH & 5FU + L + BL	16.1 months Undetermined	7.2 month on high dose & 9 month at low dose.
	Kabinnavar, 2005	5 mg/kg every 14 d	5FU +LV + B	16.6 months	9.2 months
	Tebutt, 2010 (MAX)	7.5 mg/kg every 21 d	Capecitabine	18.9 months	5.7 months

Abbreviations: *5FU/F: fluorouracil; B: Bevacizumab; d: days; IRI/I: Irinotecan; FOL/L: leucovorin; OX: Oxaliplatin; XEL: Capecitabine; BH: Bev at high dose; BL: Bev at low dose*

The single-center randomized trial by Stathopoulos with 222 patients compared the combination of Bevacizumab at a dose of 7.5 mg/kg to a bolus regimen of irinotecan and fluorouracil, both every 21 days. It is also essential to consider that current studies point toward infusion 5-FU regimens like FOLFIRI to be more beneficial than IFL. There was amendment in the protocol, a trial originally planned to compare distinct irinotecan-based therapies, randomized 117 patients to FOLFIRI plus Bevacizumab, 5 mg/kg every 2 weeks, or IFL plus Bevacizumab, at a dose of 7.5 mg/kg every 3 weeks . Updated analysis defined a significant superiority on OS (28 months v 19.8 months; P = 0.037) for the infusional treatment, versus bolus regimen[4]. At recent fluoropyrimidine plus irinotecan or oxaliplatin, combined with Bevacizumab (a monoclonal antibody against vascular endothelial growth factor), is standard first-line treatment or therapy for metastatic colorectal cancer. Before the introduction of Bevacizumab, chemotherapy with fluorouracil (F), leucovorin (FOL), oxaliplatin (OX), and irinotecan (FOLFOXIRI) showed superior efficacy as compared with fluorouracil, leucovorin, and irinotecan (FOLFIRI). In a phase 2 study, FOLFOXIRI plus Bevacizumab showed promising activity and an acceptable amount of adverse effects. Randomly assigned 508 patients

with untreated metastatic colorectal cancer to receive FOLFIRI plus Bevacizumab (control group) or FOLFOXIRI plus Bevacizumab (experimental group). Up to 12 cycles of treatment were given, followed by fluorouracil plus Bevacizumab until disease progress. The primary end point was progression-free survival[6]. Bevacizumab is broadly used as a standard treatment for mCRC; the combined treatment of chemotherapy and Bevacizumab has significantly increased the PFS and OS in patients with mCRC[7].

2.2 In Non-squamous non-small cell lung Cancer (NSCLC)

The word lung cancer refers to carcinomas that originate from the respiratory epithelium. Approximately 85 % of all lung cancers are categorized as non-small-cell lung cancer (NSCLC), 10 % are small cell lung cancer and some other histological variants account for about 5 %. A heavy smoker is considered to be at higher risk of lung cancer of about 30 % as compared with a lifetime risk of lung cancer of ≤1 % in people who have not ever smoked. Majority of patients are diagnosed with advanced, unresectable disease that is non-curable. This has a five-year survival rate of <5 %, whereas the five-year survival rate for all stages is roughly 15 %[8]. Palliative chemotherapy improves the quality of life and extends survival in patients with metastatic non-small-cell lung cancer (NSCLC). Doublet platinum-based chemotherapy has been widely accepted as evidence-based therapy for the last two decades. Attempts to surge the action of chemotherapy in a non-selective manner have involved the addition of monoclonal antibodies, in specific, antibodies directed against the epidermal growth factor receptor (EGFR) or against the vascular endothelial growth factor (VEGF). This strategy has been only marginally successful[9]. A phase II randomized trial of 99 patients with advanced or recurrent NSCLC compared Bevacizumab (7.5 or 15 mg/kg) plus up to six cycles of chemotherapy with carboplatin (area under the curve of 6) and paclitaxel (200 mg/m) every 3 weeks with carboplatin and paclitaxel alone was carried out. Patients who did not showed any progress during chemotherapy were continued on Bevacizumab alone for up to 18 cycles. The addition of 15 mg/m^2 Bevacizumab to chemotherapy resulted in an increase in time to advancement, 7.4 versus 4.2 months, compared with chemotherapy alone (P = 0.023). There was also a non-significant improvement in overall survival, 17.7 versus 14.9 months. The median duration of survival in the chemotherapy plus Bevacizumab group was 12.3 months related to 10.3 months in the chemotherapy alone group (P = 0.003)[10].

Table 2: Phase III Trials of Bevacizumab plus Chemotherapy Doublets as First-line Treatment of Non-small-cell Lung Cancer

Study	Treatment	Overall survival	Time to tumor progression (TTP)
ECOG 4599	PCL/carboplatin ± Bevacizumab 15 mg/kg	10.3 months(PCL/C) 12.3 months (PCL/C+B)	6.2 months 4.5 months
AVAil	GMB/CDDP ± Bevacizumab 7.5 mg/kg 15 mg/kg	13.2 months 13.6 months 13.4months	6.1 months 6.7 months 6.5months

AVAiL: Avastin in lung; C: Carboplatin; CDDP: Cisplatin; ECOG: Eastern Cooperative Oncology Group; GMB: gemcitabine; OS: overall survival; PCL: paclitaxel; TTP: time to tumor progress

Thus, Bevacizumab is recommended in combination with chemotherapy as first-line treatment in patients with certain clinical physiognomies[8].

Another important phase III trial was AVAPERL, in which after four cycles of chemotherapy with Cisplatin, pemetrexed, and Bevacizumab, patients were randomized to receive maintenance therapy with Bevacizumab alone or with pemetrexed and Bevacizumab. This trial revealed a benefit over the primary end-point of progression free survival (PFS) in the group receiving maintenance therapy with the doublet of drugs (6.6 months *vs.* 10.2 months). There was also an improvement in overall survival (OS) in patients cured with pemetrexed and Bevacizumab in maintenance therapy (19.8 months *vs.* 15.9 months), but the result was not statistically significant**[11].**

2.3 In Ovarian cancer

Ovarian cancer is the seventh most common cancer in women, with an estimated 225,500 new cases and 140,200 deaths globally in 2008. Indicators of the disease are non-specific, including abdominal uneasiness or fullness, dyspepsia, and swelling, which may mimic other conditions and lead to a deferral in diagnosis. Consequently, 75% of women are detected with advanced disease (International Federation of Gynecology and Obstetrics [FIGO] stage III or IV), having a median overall survival (OS) of 15–23 months and an estimated 5-year survival of just 20%. Around 90% of all ovarian cancers are epithelial ovarian cancers (EOCs) and are supposed to rise from the ovarian surface epithelium, including the fallopian tube; primary ovarian cancers also comprise ovarian-type peritoneal tumors[12].Current management of advanced stage disease includes- surgical tumor debulking, followed by adjuvant platinum- and taxane-based chemotherapy**.** Even though the introduction of platinum and paclitaxel in majority of women with advanced stage reoccur within 5 years and drug resistance appears in such women[13].

The Food and Drug Administration has approved Bevacizumab for treatment of ovarian cancer, in combination with chemotherapy, based on the outcomes of the AURELIA study. The approved protocol is Bevacizumab – in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan chemotherapy – for the treatment of women with platinum-resistant, recurring, epithelial ovarian, fallopian tube, or else primary peritoneal cancer, who have not received more than two prior chemotherapy regimens.

Table 3: Summary of efficacy data from randomized, controlled phase III trials of Bevacizumab in advanced ovarian cancer

Study	Regimen	Median PFS, months	Median OS, months
GOG-0218[12] (n = 1,873)	CP + placebo vs. CP + Bev vs. CP + Bev→Bev maintenance	10.3 vs. 11.2 vs. 14.1	39.3 vs. 38.7 vs. 39.7
ICON7 (n = 1,528) [12]	CP vs. CP + Bev→Bev maintenance	17.4 vs. 19.8	Restricted mean survival time, months
OCEANS (n = 484)[12]	CG + placebo vs. CG + Bev	8.4 vs. 12.4	44.6 vs. 44.5
AURELIA (n=361)[12]	CTx (PLD, P or Top) vs. CTx + Bev	3.4 vs. 6.7	13.3 vs. 16.6

***Bev** = Bevacizumab. **C** = carboplatin. **CR** = complete response. **CTx** = chemotherapy. **G** = gemcitabine. **OS** = overall survival. **P** = paclitaxel. **PFS** = progression-free survival. **PLD** = pegylated liposomal doxorubicin. **Top** = topotecan.*

In the intent to treat population, the primary endpoint, progression-free survival as evaluated by the investigator, was 6.8 months amongst those on Bevacizumab plus chemotherapy, compared with 3.4 months amongst those on chemotherapy alone, a highly statistically important difference. Overall survival (median Overall survival was 16.6 months vs. 13.3 months) and overall response rates (28% vs. 13%) also ideal those in the Bevacizumab plus chemotherapy group [12, 13].

2.4 In Metastatic renal cell carcinoma (mRCC)

Renal cell carcinomas (RCC) signifies less than 3% of overall cancer occurrence and death with annual incidence of approximately 200,000 worldwide and death in 100,000 cases. There has been a substantial increase in the frequency of RCC over the last few decades. Although the statistics of cases in Asia are the lowest, the ratio of incidence to mortality is higher. About 20% to 30% of patients having metastatic disease at diagnosis, and about one-third of patients undergoing nephrectomy for confined disease will develop metastases. The 5-year overall survival for patients with metastatic disease at diagnosis remains less than 20%. A better understanding of tumor biology of these cancers has brought in its wake the introduction of therapies targeting the molecular pathways involved in its growth and proliferation, which has thus lead to a paradigm shift in the treatment of metastatic RCC[14].

Table 4: Characteristics of Available Targeted Therapies for Metastatic RCC[15]

Drug	N	Median PFS (month)	Median OS (month)
Sorafenib	451	5.5	19.3
Sunitinib	335	11.0	26.4
Pazopanib	290	9.2	22.9
Axitinib	361	6.7	n/a
Tivozanib	250	11.9	n/a
Temsirolimus	20	3.8	10.9
Everolimus	277	4.9	14.8
Bevacizumab + IFN –alpha	327	10.2	23.3

IFN-a: interferon a; OS: overall survival; PFS: progression-free survival; RCC: renal cell carcinoma.

IFN-a have an overall acceptable and controllable toxicity profile, as well as a 5-month improvement in PFS, Bevacizumab plus IFN-alpha was granted FDA approval for the treatment of patients with mRCC in 2009[15]**.** Initial phase I trials with Bevacizumab involved patients with advanced cancer and provided the information that Bevacizumab can be safely administered intravenously at doses up to 10 mg/kg and some patients with RCC presented significant tumor shrinkage. A randomized phase II trial in metastatic clear cell RCC patients, who failed interleukin-2, was among the first studies to show clinical advantage in targeting the angiogenic pathway in RCC. Data from the II trial have suggested that though Bevacizumab deferred progression, it might best be combined with other therapies in RCC (such as IFN-a) to enhance results, and several trials were conducted to test this hypothesis. The European trial (known as the AVOREN trial) randomized 649 patients to receive IFN-alpha alone with placebo or Bevacizumab. Patients treated on the Bevacizumab arm had higher response rate (30 vs. 13%, $P < 0.0001$) and (TTP) Time to tumor progression (10.2 vs. 5.4 months[16].

2.5 Indications of Bevacizumab

The indications and dosage of Bevacizumab are summarized in Table-5.

Table 5: Indications and dosage of Bevacizumab

S.No	Cancer type	Combination therapy	Bevacizumab Dosage
1.	**Metastatic colorectal cancer (mCRC) first line therapy**	Bolus IFL	5 mg/kg every 2 wks
		5-FU and LV	5 mg/kg every 2wks or 10 mg/kg every 2 wks.
		FOLFOX4	5 mg/kg every 2 wks or 7.5 mg/kg every 3 wks.
2.	**Metastatic colorectal cancer (mCRC) second line therapy**	FOLFOX4	10 mg/kg every 2 wks
3.	**Non-small cell lung cancer (NSCLC) first line therapy**	Cisplatin & Gemcitabine	7.5 mg/kg every 3 wks or 15mg/kg every 3 wks.
		Carboplatin & Paclitaxel	7.5 mg/kg every 3 wks.
4.	**Breast cancer (first line therapy)**	Paclitaxel	10 mg/kg every 2 wks 7.5 mg/kg every 3 wks or
		Docetaxel	10 mg/kg every 3 wks
5.	**Metastatic renal cancer (first line therapy)**	Interferon-2a	10 mg/kg every 2 wks
6.	**Ovarian cancer**	Cyclophosphamide	10 mg/kg every 2 wks
7.	**Recurrent Glioblastoma**	-	10 mg/kg every 2 wks
FOLFOX-4 (5-FU, LV, and oxaliplatin); IFL (irinotecan, 5-FU, and LV); LV (leucovorin); 5-FU (5-fluorouracil).			

3. METHOD

A detailed literature review was carried out and articles published or presented from August 2007 to October 2014 were identified by a comprehensive investigation of electronic databases including PubMed/MEDLINE, NCBI, and BMC cancer. A subtle search strategy was performed through terms related to colorectal neoplasms, ovarian cancer, metastatic renal carcinoma, non-small cell lung cancer Bevacizumab, and randomized trials in all fields. A literature search of articles was performed using the keywords ‘‘Monoclonal antibody’’, “anti-vascular endothelial growth factor”, ‘‘Bevacizumab’’, and ‘‘Avastin’’.

3.1 Selection Criteria

The goal of this study was to identify published articles on Bevacizumab containing data on various clinical trials performed for various types of cancers such as metastatic colorectal cancer, ovarian cancer, Metastatic renal cancer, non-small cell lung cancer. These articles provided the information about various types of studies conducted, end point of the studies and various combination therapy i.e. chemotherapeutic agents and Bevacizumab that are used for treating such type of cancers.

4. CONCLUSION

Bevacizumab is an angiogenesis inhibitor that has shown favorable results in the treatment of various cancers. Bevacizumab appears to be safe and effective in the short term. The substantiation for efficacy and safety is increasing. The drug has been approved for different indications such as metastatic colorectal cancer, non-small cell lung cancer, metastatic renal cancer, ovarian cancer and the data from various studies indicated that the drugs is useful in improving the progression free survival (PFS) and overall survival (OS) in patients having such type of cancers. Bevacizumab is an effective agent for first-line treatment for metastatic colorectal cancer. The physicians prescribing this drug are also required to be aware of their responsibility towards the patient. This not only includes the risks associated with the use, but also the cost problem and the availability of approved drug to the Indian patients. As it has been found from the above studies that drug has proven to improve the overall survival of the patients having metastatic colorectal cancer, non-small cell lung cancer, metastatic renal cancer, ovarian cancer, now also been given for cervical cancer and recurrent Glioblastoma, but the drug is too expensive that majority of Indian patients are not able to receive the Bevacizumab therapy. So there is required to develop the marketing strategy that would increase global availability of drug to Indian patients that might be reduction in the cost of therapy or creating awareness among masses about sign and symptoms of cancer or by conducting or organizing continuous medical education programs and cross specialty meetings between various oncologist, general physicians, pathologist etc. for updating the knowledge and throwing some light on emerging trends in the field of oncology that would prove to be beneficial in the therapy area for cancer.

5. FUTURE PERSPECTIVE

The role of Bevacizumab in the treatment of breast cancer is not evidently defined by the current trials; even though there is improvement in progression free survival (PFS), this has not turned into improvement in overall survival. Additional studies are required to be done to address whether longer-term usage of Bevacizumab will show substantial progress in overall survival for patients with metastatic breast cancer. At present, the role for anti-angiogenic agents in the treatment of breast cancer is not well demarcated. In the upcoming years it is supposed that some biomarkers might be developed that may help better identify which patients will have advantage from certain treatments and will therefore be able to make available individualized therapy for patients.

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REFERENCES

1. Filis KH, Beijnen JH and Schellens JHM, Bevacizumab- Clinical Pharmacology: Concise Drug Reviews, Oncologist. 2010, 15, 819-825.

2. Kashima YY, Ouchi KF, et al, Biomarkers for antitumor activity of Bevacizumab in gastric cancer models, BMC Cancer. 2012, 12 (37): 1-11.

3. Cuppone F, Bria E, et al, Biomarkers for antitumor activity of Bevacizumab in gastric cancer models, J. Exp. Clin. Cancer Res. 2011, 30 (54):1-9.

4. Macedo LT, Bacellar CL, et al, Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups, BMC Cancer. 2012, 12(89): 1-8.

5. Chen Y, Yang Q, et al, Efficacy of Adding Bevacizumab in the First-Line Chemotherapy of Metastatic Colorectal Cancer: Evidence from Seven Randomized Clinical Trials, Gastroenterol. Res. Pract. 2014, 1: 1-9.

6. Loupakis F, Cremolini C, et al, Initial Therapy with FOLFOXIRI and Bevacizumab for Metastatic Colorectal Cancer, N. Engl. J. Med. 2014, 371:1609-1618.

7. Cai J, Huang F, et al, Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer treated with Bevacizumab: a systematic review and meta-analysis, World J. Surg. Onc. 2013, 11(306): 1-8.

8. Pallis AG, A Review of Treatment in Non-small-cell Lung Cancer, Eur. Oncol. Haematol. 2012, 8(4):208–12.

9. Vokes EE, Salgia R and. Karrison TG, “Evidence-based role of Bevacizumab in non-small cell lung cancer.” Ann. Oncol. 2013, 24 (1), 1-4.

10. Sandler A, Bevacizumab in Non-Small Cell Lung Cancer, Clin. Cancer Res. 2007, 13(15):4613s-4616s.

11. Lauro S, Onesti C, et al, The Use of Bevacizumab in Non-Small Cell Lung Cancer: An Update, Anticancer Res. 2014, 34: 1537-1546.

12. Aravantinos G and Pectasides D, Bevacizumab in Combination with Chemotherapy for the Treatment of Advanced Ovarian Cancer: A Systematic Review, J. Ovarian Res. 2014, 7(57), 1-9.

13. Singh H, Bevacizumab and ovarian cancer, Ther. Adv. Med. Oncol. 2013, 5(2):133–141.

14. Bharthuar A, Metastatic renal cell carcinoma: Current scenario and future trends, South Asian J. Cancer. 2012 Jul-Sep; 1(1): 30–35.

15. Logan JE, Rampersaud EN, Systemic Therapy for Metastatic Renal Cell Carcinoma: A Review and Update, Rev. Urol. 2012, 14(3/4):65-78

16. Choueiri TK, Metastatic renal cell carcinoma: A guide to therapy based on current evidence, Urol. Ann. 2009, 1(19):1-6.