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Research Article

## Role of Vascular Endothelial Growth Factor Receptor Inhibitors in Refractory Cervical Cancer

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### Abstract

This review article focuses on the past and future aspects of vascular endothelial growth factor inhibitors in Cervical Cancer. Vascular endothelial growth factor (VEGF)-mediated angiogenesis is considered to play a vital function in the tumor development and metastasis. Therefore, VEGF-inhibitors are being actively considered as prospective anticancer treatment. The most widely studied tyrosine kinase inhibitors that target VEGF or anti- VEGF monoclonal antibodies and receptors, promise significant results in clinical trials.

**Keywords:** Vascular Endothelial Growth Factor; Tyrosine Kinase Inhibitor; Angiogenesis; Human Papilloma Virus; Anti-Angiogenesis Factor

### Abbreviations

FDA: Food and Drug Administration;  
GOG: Gynecology oncology group;  
HPV: Human papillomavirus;  
MAPK: Mitogen-activated protein kinase;  
PI3K: Phosphoinositide 3-kinase;  
PDGFR: Platelet-derived growth factor receptor;  
RTK: Receptor Tyrosine Kinase;  
VEGF: Vascular endothelial growth factor;  
VEGFR: Vascular endothelial growth factor receptor

### Introduction

Cervical cancer is the 3rd most common cancer in women, worldwide, and it is the leading cause of death of women in developing countries. However, in the United States, cervical

cancer is relatively uncommon. Over the past few decades, the rate of invasive cervical cancer has been declining continuously in the US. The rate has decreased by 2.1 % per year, in women younger than fifty years, and 3.1%, in 50 years of age and older. This trend is achieved by mass screening with

Pap-tests and availability of preventive measures, such as vaccinations [1].

Cervical cancer is the cancer, which arises from the cervix, the narrow opening into the uterus from the vagina. A portion of the uterus, which extends into the vagina, also known as ectocervix, is covered with squamous cells. Cervical canal is also made up of another cell type, called columnar cell. They are also termed as endocervix. These cells meet at a junction, called "transformation zone", which is the most possible location for abnormal or precancerous cells to develop. Approximately, 80-90% of cervical cancers are squamous cell cancers, and adenocarcinoma is the second most common type of cancer. Adenocarcinoma originates from the glands that produce mucus in the endocervix. Incidences of adenocarcinoma are aggregating, particularly in younger women. The mortality rate of the cervical cancer has been declining, because of the awareness program and early detection, through diagnosis by the use of the Pap smear test. In most cases, Human papillomavirus (HPV) is the prime cause of cervical cancer. There are several types of HPV, most of which are considered of low-risk and not responsible for cervical cancer. High-risk HPV generates abnormalities, responsible for cancer. HPV-16 and HPV-18 are known as high risk HPV, which are basically responsible for causing cervical cancer in 70 % of the cases. In USA, it is categorized as one of the common sexually transmitted infection [2].

All over the world, the pace of new cases of cervical cancer is estimated to be about 465,200 per year, in which developed countries contribute around 20%, whereas 80% is done by the developing nations. Cervical cancers are presently, 7.3 % of all the human cancers, worldwide. Incidence and mortality rate of cervical cancer has been changed, due to the availability of screening programs and invention of HPV vaccination, which is easily available in developed countries. This is the only reason of the reduction of incidence and mortality rate of cervical cancer, over the past 50 years in developed states. In continents, like Africa, Asia and outside Japan, Central and South America, cervical cancer is prominent among women with 20-30% of the incidence, worldwide. Epidemiology of cervical cancer indicates that women who have had multiple sexual partners or have had male sexual partner at high risk (i.e. males, who have had sexual intercourse with many sexual partner or had intercourse at early age), or women who have had first intercourse at early age, smoking, long term use of contraceptives, dietary factors, and immune-suppressed status are at higher risk of Cervical cancer. There are some infectious agents, responsible for cancer, such as syphilis, herpes simplex virus 2, chlamydia trachomatis etc. [3].

The primary causal agent of cervical cancer in two types of cancer, called squamous cell cancer and adenocarcinoma, is

HPV infection. Approximately, 100 types of HPV are present, in which forty different types of HPV affect the genital part. Fifteen types of HPV are designated as high risk factors for cervical cancer, which include types 16 and 18. These two are main causal agent for cervical cancer, in about 7 out of 10 cases. There are some vaccines, now available, to prevent HPV vaccines. It protects against the HPV strains, but it is unable to protect completely. It will take some years, before the debut of the vaccine sustains a major effect on cutting down the number of instances of cervical cancer. It is however, important to carry along with cervical cancer screening. Main symptom of cervical cancer is abnormal vaginal bleeding, which can happen between periods, after and during copulation; and at any time after menopause. Some adult females have a vaginal discharge, which has an unpleasant smell and uneasiness or pain, during intercourse. Symptoms also include pelvic or back pain, pain during urination and blood in stool or urine. These symptoms can be non-specific [4].

Cervical Cancers are classified, based on origin, as follows:

- i) Squamous cell carcinoma: Originates from cells that lines the surface of the cervix. It comprises about 80% of all the cervical cancers.
- ii) Adenocarcinoma: It originates from the gland's cell. Percentage of adenocarcinoma cases has climbed up, since 1970s.
- iii) Adenosquamous carcinomas: Sometimes patients can have both squamous and adenocarcinoma types of cervical cancer, also known as adenosquamous carcinomas.
- iv) Small cell and neuroendocrine carcinoma: There are some other type of cancers, called small cell and neuroendocrine carcinoma. However, they all are very rare [5].

VEGF/VEGFR inhibitors are agents that constrain the action of VEGF/VEGFR, which is responsible to make new blood vessels from the existing blood vessels, the process called as angiogenesis. Abnormal angiogenesis is the condition that occurs in cancer, other involves inflammation and progressive eye conditions. Some monoclonal antibodies and particularly, tyrosine kinase inhibitors are used as VEGFR inhibitors [6]. During the last few years, several members of the VEGF family have been described, namely the VEGF-A, B, C, D, E and placenta growth factor (PlGF) among which, VEGF-A (121 amino acids) plays a role of prime importance in angiogenesis. VEGF is a 45 kDa glycoprotein, homodimeric, basic, with the potential to bind heparin. The three-dimensional structure of VEGF has been recently determined, by X-ray diffraction, and NMR spectroscopy [7]. There are three types of VEGF receptors, called 1, 2, and 3 [8]. VEGFR-1 is responsible for the functionality of hematopoietic stem cells and movement of the monocytes and macrophages [9].

VEGF ligands facilitate their angiogenic effect, when comes in contact with VEGF receptors and multiplies with consecutive signal transduction. Ligands bind with the primary 3 receptors and 2 co-receptors. VEGFR-1 and 2 are generally associated with angiogenesis. VEGFR-3 is associated with lymphangiogenesis [10]. In abnormal angiogenesis condition, the formation of blood is inhibited by specific monoclonal antibodies used as VEGFR inhibitors, particularly to treat cancer [11].

### Mechanism of Action

In case of tumor and metastatic propagation, angiogenesis is the main event and VEGF pathway is easily recognized to determine this procedure. The VEGF and VEGFR have multiple ligands and receptors, having specific ligands-receptor binding sites, functions and cell type expression. Once VEGF receptors are activated, they in turn, start activating a pathway of signals that encourage the endothelial cell growth, migration and survival from pre-existing vasculature. VEGF also facilitates permeability of vessels, and has been connected to a malignant effusion. In recent years, the mobilization of endothelial cells from the bone marrow to the particular site of neovascularization has been an important role of VEGF. The main role of VEGF, in stimulating tumor angiogenesis and the pathogenesis of human cancers, has prompted the reasonable configuration and advancement of agents that specifically focus on this pathway. In the past few years, anti-VEGF antibody, e.g. Bevacizumab, used in combination with chemotherapy, showed significant clinical benefits in cancer patients [10]. The VEGF factors and receptors play a vital role in angiogenesis. There are some developed agents, which direct against VEGF or VEGF receptors, e.g. low molecular weight tyrosine kinase inhibitors, results in a barrier of intracellular signaling, by ATP-mimetic proteins that binds to the ATP binding catalytic site of the tyrosine kinase domain of VEGFRs. These agents are used in many clinical and developmental trials, nowadays [12].

Techniques, which have been used to block the normal VEGF pathway, are as follows:

- i) Deactivating monoclonal antibodies against VEGF/VEGFR.
- ii) Tyrosine kinase inhibitors of VEGF.
- iii) Soluble VEGF receptor, which acts as trapping agent for VEGF and;
- iv) Ribozymes, which specially target on VEGF mRNA.

In later age, FDA has approved bevacizumab as an anti-VEGF monoclonal antibody, as significant results have been presented in Phase III, in combination with other chemotherapeutic agents in many cancers, namely colorectal cancer [13].

The FIGO (International Federation of Gynecology and Obstetrics) staging for cervical cancer, are categorized as follows:

- Stage Ia Cervical carcinoma: Preclinical invasive carcinoma that can be diagnosed only by means of microscopy.
- Stage Ib Cervical carcinoma: A clinically visible lesion that is confined to the cervix uteri.
- Stage Ib1: Primary tumor, not greater than 4.0 cm in diameter.
- Stage Ib2: Primary tumor greater than 4.0 cm in diameter.
- Stage IIa Cervical carcinoma: Tumor has spread into the upper two thirds of the vagina, without parametrial invasion.
- Stage IIb Cervical carcinoma: Extension into the parametrium, but not into the pelvic sidewall.
- Stage IIIa Cervical carcinoma: Extension into the lower one-third of the vagina, without spread to the pelvic sidewall.
- Stage IIIb Cervical carcinoma: Extension into the pelvic sidewall and/or invasion of the ureter, with the latter, resulting in a non-functioning kidney or hydronephrosis.
- Stage IVa Cervical carcinoma: Extension of the tumor into the mucosa of the bladder or rectum.
- Stage IVb Cervical carcinoma: Spread of the tumor beyond the true pelvis, and/or by metastasis, into the distant organs [14].

### Current status of knowledge

Improved survival rate of patients with advanced cervical cancer, after incorporation of Bevacizumab.

In recent years, there has been a dramatic change, due to the screening and DNA testing for high risk HPV types. Bevacizumab is a VEGF-neutralizing monoclonal antibody, and pre-treated with recurrent cervical carcinoma. In GOG 240, a phase-3 trial was performed in the United States and in Spain, by the Gynecologic Oncology Group and Spanish Research Group for Ovarian cancer, for the investigation of the administration of bevacizumab. It was validated in a randomized phase III trial of cisplatin plus paclitxel, with and without bevacizumab, versus the non-platinum doublet of topotecan plus paclitxel, with and without bevacizumab, in stage IVB, recurrent or persistent carcinoma of the cervix.

In this study, 452 patients were randomized in 2-by-2 factorial design and administrated with chemotherapy, with or without bevacizumab, at a dose of 15mg/kg of body weight. Chemotherapy includes cisplatin at a 50 mg/m<sup>2</sup> of the body surface and paclitaxel at a dose of 135 or 175 mg/m<sup>2</sup> or topotecan at a dose of 0.75 mg/m<sup>2</sup> on day one to three, plus paclitaxel at a dose of 175 mg/m<sup>2</sup> on the first day. This cycle was repeated after every 21 days, until disease progression. Primary outcomes were overall survival and a 30% of the hazard ratio of death was seen, which was clinically important. All sets of patients were similarly randomized, with respect to age, performance status, histologic finding, and use or without use of a radiosensitizing platinum agent, and disease status. The combination of Topotecan and paclitaxel was not more relevant to cisplatin-paclitaxel (mortality rate: 1.20). Addition of bevacizumab, in chemotherapy was more efficacious than chemotherapy alone, regardless of the type of combination chemotherapy, used to improve the overall survival. (e.g. 17.0 months vs 13.3 months; and risk of death rate, 0.71; 98% confidence interval, 0.54 to 0.95; P=0.004 in a one-sided test) and response rates (48% vs 36%, P=0.008). Such appreciable response rate and survival benefits were also accompanied with more frequent adverse events, namely hypertension of grade 2 or higher (25% vs 2%), thromboembolic events of grade 3 or higher (8% vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%).

Overall, conclusion of this clinical trial shows combination therapy with bevacizumab, as an angiogenesis inhibitor, in patients with advanced cervical cancer, results in better response rate and progression free survival and an improvement of 3.7 months in median survival [15].

### Role of Receptor tyrosine kinase (RTK) inhibitors in local and advanced cervical cancer

RTK (Receptor tyrosine kinase) inhibitors e.g. sunitinib, sorafenib, pazopanib, cediranib have been tested in phase I-II of clinical trials in cervical cancer. When 19 locally progressive and metastatic cervical cancer patients were treated with sunitinib, results have been watched with no responses and about 84% of the stable diseased condition and higher incidence of fistula development in a phase II clinical trial. In another study, sorafenib, in combination with cisplatin and radiation has been tested in DDPDR0-002 trial (study ID number) in T1b-3b N0/1 stage of cervical cancer. Imatinib mesylate, an inhibitor of ABL (ableson gene at chromosome 9) tyrosine, that inhibits PDGFR (Platelet-derived growth factor receptor) and c-kit has been studied in a recurrent cervical cancer, venting PDGFR- $\alpha$ , but no reactions have been noticed, although, less than 10 % of tumor cells expressed PDGFR- $\alpha$  in all enrolled patients. In a phase II study; combination of pazopanib or lapatinib (Epidermal Growth Factor Receptor Inhibitor) was carried in 228 stage-IV pre-treated cervical cancer patients. This combination was not

continued, because of ineffectiveness and toxicity of lapatinib monotherapy. Moreover, pazopanib, as a single agent, had improved response rate and progression free survival over lapatinib. A different VEGF receptor inhibitor, cediranib, was tested in combination with carboplatin, paclitaxel or temsirolimus in -phase- II (NCT01229930) and Phase-I trials (NCT01065662) in advanced cervical cancer. The role of other VEGFR inhibitor, such as brivanib, and fibroblast growth factor (FGF) receptors are presently under clinical assessment (NCT01267253).

In current scenario, existing preclinical and clinical data information are playing important role in the development and progression of cancer. Below mentioned, Table 1 shows the data related to clinical trials of advanced cervical cancer, when treated with biological agents; and Table 2 reports data related to ongoing clinical trials.

Patients enrolled	Phase	Regimen	Target	Clinical Endpoint/ORR	Toxicity
450	III	Bevacizumab (15mg/kg iv every 21 days) with or without four chemotherapy regimens	VEGF	OS 17 months in bevacizumab arms versus 13 months in the chemotherapy arms	Treatment with B was associated with more grade 3-4 bleeding (5 vs 1%) thrombosis/embolism (9 vs 2%), and GI fistula (3 vs 0%)
60	II	Bevacizumab (10mg/kg iv every 2 weeks for three cycles) in combination with definitive radiotherapy and cisplatin chemotherapy	VEGF	No data	15 (31%) protocol-specific treatment related AEs within 90 days of treatment start; the most common were hematologic (12/15; 80%). No treatment related SAEs
27	II	Bevacizumab (15mg/kg iv every 21 days) with topotecan and cisplatin	VEGF	ORR: 33.3%	Grade 3-4 hematologic toxicity was common (thrombocytopenia 82%, leukopenia 74%, anemia 63%, neutropenia (56%). Most patients (78%) required unanticipated hospital admissions for supportive care and/or management of toxicities
19	II	Sunitinib 50 mg daily per os	VEGF	No objective responses. Median TTP: 3.5 months	High rate of fistula development (26%)
30	II	Gefitinib 500mg daily per os	EGFR	No objective responses, six (20%) patients experienced stable disease with a median duration of 111.5 days. Median TTP was 37 days and median OS was 107 days.	Gefitinib was well tolerated, the most common drug-related AEs were diarrhea, acne, vomiting, and nausea. No grade 4 events.
28	II	Erlotinib 150mg daily per os	EGFR	No objective responses with four (16%) achieving stable disease; only one patient had a PFS $\geq$ 6 months (4%)	Grade 3 related toxicities included diarrhea, nausea, emesis, dehydration and anorexia. One patient experienced grade 4 renal toxicity.

38	II	Cetuximab 400mg/m <sup>2</sup> i.v. initial dose followed by 250 mg/m <sup>2</sup> weekly	EGFR	No objective responses with five patients (14.3%) survived without progression for at least 6 months. Median PFS and OS times were 1.97 and 6.7 months, respectively.	Grade 3 adverse events at least possibly related to cetuximab included dermatologic events, GI, anemia, constitutional symptoms, infection, vascular events, pain, and pulmonary, neurological, vomiting and metabolic events. No grade 4 events
38	II	Temsirolimus (25mg i.v. weekly in 4 week cycles)	mTOR	One patient experienced a partial response (3.0%). 57.6% stable disease. Median PFS: 3.52 months.	No toxicity grade 3 observed. Adverse effects were mild-moderate in most cases and similar to other temsirolimus studies.
36	III,R	Hydralazine and valproate (HV) added to cisplatin topotecan (hydralazine at 182mg for rapid, or 83 mg for slow acetylators, and valproate at 30mg/kg, beginning a week before chemotherapy and continued until disease progression)	HDAC	4PRs to CT + HV and 1 CT + PLA. 29% and 32% stable disease, respectively.	Low incidence of grades 3 and 4 toxicity in both arms. G2/3 thrombocytopenia, edema, drowsiness and tremor were statistically higher in CT+HV arm.
40	II,R	rAd-p53 combined with chemotherapy (PCG arm) vs chemotherapy alone (CG arm)	Proteasome	ORR 95% in PCG arm versus 75% for the CG arm. 1-year OS; 90% and 65%, respectively	Fever was found in 90% of the PCG patients (mild to medium grade). No serious adverse events relative to rAd-p53 were observed

**Table 1.** Data related to clinical trials of cervical cancer, using biological agents. [16] Abbreviations used- ORR: Overall Response Rate; OS: Overall Survival; TTP: Time to progression; PFS: Progression-free survival; iv: intravenously; R: randomized; GI: gastrointestinal.

Study Number	Phase	Estimated number of subjects	Regimen	Target	Primary end point
DDPDRO-002	I/II	30	Sorafenib with radiation and cisplatin	Multikinase	Determine the biologic activity of sorafenib in cervix cancer
NCT01229930	II	130	Carboplatin and paclitaxel with or without cediranib maleate	VEGF	Overall progression-free survival
NCT01065662	I/IB	50	Temsirolimus with cediranib	VEGF	Maximum tolerated dose of cediranib with temsirolimus
NCT01267253	II	51	Brivanib alaninate monotherapy	VEGF and FGFR	Progression-free survival for atleast 6 months, objective tumor response, adverse events as assessed by NCI CTAE v4.0
NCT00957411	II	76	Cisplatin and pelvic radiotherapy with or without cetuximab	EGFR	Recurrence-free survival at 2 years

NCT01158248	II	50	Panitumumab with cisplatin and radiotherapy	EGFR	Progression-free survival at 4 months and rate of skin and/or gastrointestinal toxicity CTCAE grade 4 at 4 months
NCT01281852	I/II	66	Veliparib given with paclitaxel and cisplatin	PARP	Toxicities and objective tumor response
NCT01266447	II	60	Veliparib with topotecan and filgrastim or pegfilgrastim	PARP	Objective response, overall survival time, progression-free interval
NCT01237067	I	72	Olaparib with carboplatin	PARP	Pharmacokinetics and pharmacodynamic effects of the sequence of administration of olaparib and carboplatin and the schedule-associated safety of the combination
NCT01076400	I/II	7	MK-1775 with cisplatin and topotecan	WEE1	Objective response rate and maximum tolerated dose.
NCT01711515	I	18	Ipilimumab after adjuvant chemoradiation	CTLA-4	Maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of adjuvant ipilimumab

**Table 2.** Ongoing clinical trials of targeted agents in cervical cancer [16].

There are several studies still going on, regarding the activity of VEGFR inhibitor in the first line, as well as relapsed cases of cervical cancer [16].

Inhibition of VEGF can be an attractive treatment because it is highly specific and less toxic. VEGF inhibitors offer a way to control a heterogeneous tumor population, by determining a relatively homogeneous endothelial population. Ideally, these inhibitors should control tumor growth and bring a dormant state, in which pro-angiogenic and antiangiogenic factors are balanced, and tumor growth is controlled. Antiangiogenesis agents mainly stabilize the growth of tumor, which can be suited for long term therapy. However, the best suited selection of patients for VEGFR inhibitor treatment should be determined. The most commonly used method for this selection is microvessel density measurement in tissue samples for tumor angiogenesis. However, this might not be the best method of suitable treatment, because measurements may require multiple biopsies and results are best subjective [17].

**Antiangiogenic agents a source of hemostatic regulator of tumor angiogenesis:**

Hemostatic factors are parts of a system, which maintains the

vascular integrity and controls the blood loss from the body. It controls the aggregation of local platelet and a process of conversion of soluble fibrinogen to insoluble fibrin polymer; and dissolution of fibrin. Although, these factors also participate in physiological processes, such as tissue remodeling, wound repair, development, reproduction, angiogenesis and inflammation, the process of angiogenesis is harmonized and controlled by hemostasis process. Inhibitors of angiogenesis are present within platelets as secret fragments of hemostatic proteins and calculate the preclinical and experimental indication for their ability to inhibit tumor angiogenesis, as well as their potential to be cancer promoting agents. Table 3 summarizes the pro and antiangiogenic factors in platelet granules.

Proangiogenic factors	Antiangiogenic factors
Vascular endothelial growth factor-A, -C	Thrombospondin-1
Fibroblast growth factor-2	Transforming growth factor $\beta$ -1
Hepatocyte growth factor	Platelet factor-4
Angiopoietin-1	Hepatocyte growth factor-derived fragments
Platelet-derived growth factor	Plasminogen (precursor of angiostatin)
Epidermal growth factor	$\alpha$ 2-antiplasmin
Insulin-like growth factor-1, -2	Plasminogen activator inhibitor-1
Insulin-like growth factor binding protein-3	Heparin binding fibronectin fragments
Vitronectin	Epidermal growth factor fragment
Fibronectin	Endostatin
Fibrinogen	High-molecular-weight kininogen (precursor of kininostatin)
Heparanase	Tissue inhibitor of metalloproteinase-1, 2
Thymidine phosphorylase	
Sphingosine 1-phosphate	

**Table 3.** Platelet-derived pro- and antiangiogenic factors.

The process of platelet activation usually begins, when they adhere to the exposed collagen at the site of vascular injury, directly through collagen receptor GPIV and indirectly, by von Wilbrand factor that acts via GPIb-IX. This adhesion leads to the activation of GPIIb/IIIa, platelet aggregation and platelet plug formation, as the final result of hemostasis procedure that is generally followed by coagulation process.

Angiogenesis is initiated in concert with coagulation, when the increased permeability of the damaged vessel results in extravasation of adhesive plasma glycoproteins, such as fibrinogen and fibronectin, and formation of a temporary scaffold for migrating endothelial cells [18]. Activation of platelets leads to platelet degranulation with its proangiogenesis as well as antiangiogenesis products, namely VEGF. Vascular endothelial growth factor is also released from endothelial cells of vasculature bed, together with von Wilbrand factor. Sequestered forms of VEGF are also present in the matrix of sub-endothelium that is activated indirectly by thrombin, as the main product of coagulation cascade, through proteinase activity, promoted by thrombin. VEGF that has been produced during coagulation by above-mentioned pathways, in turn, activates

the fibrinolytic activity and tissue plasminogen activator, as the main anti thrombotic mediators in the body.

It has been proposed that the hyperpermeability of the tumor vasculature, caused by tumor- derived angiogenic factors, may result in exposure of the subendothelium and thus, facilitate platelet adhesion [19]. This process induces a vicious cycle to produce more VEGF, with resultant tumor progression.

### Current approaches and future prospects of Angiogenesis inhibitors

Angiogenesis plays an important role in tumor growth. There are several ongoing projects for the drug development, in which some are in preclinical stage, some in clinical, and are achieving approval from the US Food and Drug Administration. Many regulatory and signaling molecules, leading to the angiogenesis process, are of interest, including growth factors (e.g. VEGF, PDGF and FGF), receptor tyrosine kinases, and transcription factors, such as hypoxia inducible factor, and molecules involved in mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling. These signaling molecules define key molecular mechanisms and novel therapies that are on the verge of describing antiangiogenic tumor therapy [20].

### Side effects of angiogenesis inhibitor in the treatment of cancer.

Anti-angiogenic drugs, along with anti-VEGF agents, have shown their role in the armamentarium against cancer, due to which, the incidences of unexpected toxicities have been experienced. There are some drugs, which are approved by FDA and are usually used for cervical cancers, such as Bevacizumab, along with chemotherapy. Side effects of angiogenesis inhibitors are hypertension, rash on dry skin, Hand-foot syndrome, diarrhea, Fatigue, Low blood counts, wound healing problem, etc. Side effects can vary with each and every patient, as well as the type and mechanism of action of the drug itself. Sometimes, angiogenesis inhibitors may cause serious heart attacks, bleeding, blood clots or, heart failure. People at higher risk of developing danger for these conditions should talk about the hazards and benefits of these agents, along with ways to monitor these risks [21].

### Modern approach of locally advanced cervical cancers.

Radiation was the routine treatment for advanced cervical carcinoma, in earlier times. Although, after years of studying, multi-modality treatments acted as an alternative in phase III trials, and routed towards chemo-radiation therapy. This combination therapy added about 12% benefit in 5 years survival alone. When neoadjuvant chemotherapy is combined with surgery, 15% increase in 5 year survival rate has been observed,

compared with radiation alone. Benefits in survival rate are comparatively high, with the present chemo- radiation therapy, based on cisplatin. Even with these promising results, there is a room for improvement in the 5 year survival of patients treated with chemo-radiation. Evaluation of additional approach is required for the chemo-radiation, after neoadjuvant chemotherapy. Use of radiosensitizers, other than cisplatin, and targeted therapy, in addition to neoadjuvant combination chemotherapy, surgery and concurrent chemoradiation, may in the time improve the current status of cisplatin-based chemo- radiotherapy. However, it is difficult to forecast the dramatic increase in the rate of survival, even with the optimum combination of cytotoxic drugs, surgery and radiation [22]. Recent progresses in molecular basis of cancer cell proliferation and progression and most importantly, understanding angiogenesis and its role in tumor progression, has led to new drug development, targeting these pathways as a potential treatment modality and adding more efficacy to conventional treatment, together with few adverse events, especially when administered in clinically fit patients.

## Conclusion

Some anti-cancer signal transduction inhibitor drugs, which act as an anti-angiogenic drugs, as well as monoclonal antibodies, targeting VEGFR, are clinically approved for cancer therapy and mostly accepted, since the last 20 years. It may be about to make a significant mark on clinical oncology, and it increases awareness of the importance of interactions between tumor and host. Anti-angiogenesis are essential for the reduction of tumor growth, and it can be reduced only by the inhibition of VEGF pathway. Tyrosine Kinase inhibitors, as well as monoclonal antibodies, targeting VEGFRs, are mostly used for this purpose. These are easily available in the market today, such as Sunitinib is available and commonly used TKI that inhibits VEGR from binding to its receptor and Bevacizumab, as a monoclonal antibody that shows clinical benefit in many different tumor types. A large number of small molecule inhibitors of VEGFR tyrosine kinase are currently active in therapy and progression and they signify a new prospect for the treatment of patients with different types of tumors, which is refractory or relapsed after conventional treatment approaches. Ongoing and new therapies are coming up, and are well-designed for trials, which will improve the clinical application of these drugs.

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