CHAPTER

67

Targeted Therapies in Solid Tumors : Current Concepts

V. Talwar

Introduction

Molecularly targeted therapies for the treatment of patients with solid tumors continues to evolve. Two cell signal transduction pathways regulate the development, proliferation, and metastasis of solid tumors: the human epidermal growth factor (HER) receptor pathway and the vascular endothelial growth factor (VEGF) receptor pathway. Pharmacologic agents with distinct indications and methods of administration target the HER and VEGF molecular pathways. Each of the pharmacologic agents that target these pathways has unique indications and means of administration.

Molecular Pathways

Human Epidermal Growth Factor Receptors

The HER family of receptors consists of four structurally related transmembrane receptors: HER 1 (epidermal growth factor receptor [EGFR] or cerb81), HER2 (cerb82 or HER2/neu), HER3 (cerb83), and HER4 (cerb84). HER receptor tyrosine kinases (TKs) have an extracellular ligand-binding domain, a transmembrane domain and an intracellular tyrosine kinase (TK) domain.[1] HER family dysregulation is associated with atypical cell behavior and current investigations are focused specifically on the role that EGFR signaling pathways play in carcinogenesis.

EGFR is expressed in healthy cells of germ cell derivation, espically those of epithelial origin, EGFR overexpression is associated with cancers of the colon, head and neck, pancreas, lung (non-small cell), breast, Kidney, bladder and Gliomas. Alterations in EGFR activity correlate with disease progression, poor prognosis and the development of resistance to cytotoxic agents.[2]

EGFR activation begins when an extracellular ligand binds to an EGFR monomer (inactive protein). Several stimulatory ligands bind with EGFR, including the epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α). The ligand-bound receptor dimerizes or pairs with other monomers on the cell surface. EGFR can pair with another EGFR (homodimerization) or another member of the HER family (heterodimerization). Dimerization promotes transmembrane signal transduction, resulting in intracellular TK activity and phosphorylation.[2] A phosphate group from adenosine triphosphate (ATP) is transferred to the tyrosine residues on the signal transduction molecules. The phosphorylated TK residue becomes a binding site for key signal transducers that activate multiple downstream signaling pathways. Significant downstream pathways include Ras-Raf-

Mek-MAPK, which regulates gene transcription and proliferation, and the P13K/Akt signaling pathway, which governs cell survival.[2] The specific binding ligand and the coreceptor to which EGFR is dimerized determine the signaling pathways that EGFR activates. Multiple factors contribute to upregulation of EGFR signaling, including overproduction of ligands by the tumor cell, overexpression of EGFRs on the cell surface, and mutations that initiate EGFR activity independently of ligand binding.[2]

HER2, like EGFR, is a TK receptor that is expressed on a variety of normal cells. The HER2 receptor has no known ligand and participates in signal transduction by forming heterodimers with other HER family receptors. HER2-containing heterodimers exhibit strong ligand binding, which enhances downstream signaling and delivery of proliferative signals to the nuc1eus. Overexpression of HER2 results in the formation of HER2 homodimers that are also extremely active.[3] Gene amplification (generation of more than the normal two gene copies) and overexpression of HER2 occur in approximately 25% of breast cancers and are associated with aggressive tumor behavior and decreased overall survival.[3]

Activation of HER2 and EGFR receptors triggers multiple signaling pathways that play a critical role in cellular growth and proliferation. Tumor cells express VEGF, a protein responsible for the development of new blood vessels (angiogenesis), as a result of EGFR signaling.

Vascular Endothelial Growth Factor

Like normal cells, cancer cells depend on an adequate blood supply to provide oxygen, nutrients, and other elements essential for survival and growth. Solid tumors can absorb sufficient nutrients and oxygen by diffusion until they measure 2 to 3 mm; further growth requires the formation of new blood vessels or angiogenesis.[4]

Angiogenesis is a normal physiologic response during wound healing, menstruation, and embryonic development. It is a dynamic, complex process regulated by a number of factors. VEGF, a member of the platelet-derived growth factor family, has a well-documented role in tumor angiogenesis. A number of solid tumors express VEGF; among them are glioblastomas and colon, gastric, breast, lung, brain, hepatocellular, and bladder cancers.

Numerous stimuli increase VEGF expression: genetic events, hypoxia, nitric oxide, and growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF-1). The primary source of VEGF is the tumor itself, but associated stromal and vascular endothelium cells also express VEGF, especially in the presence of Hypoxia.[4]

Angiogenesis is a multistep process that begins with VEGF binding to VEGFR1 (FLT1) and VEGFR2 (KDR or Flk-1), which are located on endothelial cells found in blood vessels. Receptor activation leads to TK phosphorylation, inducing multiple downstream pathways and production of proteins that promote angiogenesis. VEGF signaling increases the permeability of surrounding vasculature, proliferation of endothelial cells, and degradation of the extracellular matrix, which promote endothelial cell migration. Finally, VEGF inhibits endothelial cell apoptosis by stimulating the expression of antiapoptotic factors Bcl-2 and BcI-1. The resulting unstable vasculature is tortuous, dilated, and leaky. Despite the development of new vasculature, the tumor remains hypoxic, and angiogenesis is further stimulated. The unstable characteristic of the tumor vasculature may contribute to ineffective delivery of cytotoxic agents, resulting in poor response.[4]

Novel Strategies for Molecular Targeting

Signaling pathways present multiple opportunities for intervention. In the extracellular domain, altering the ligand or the receptor would prevent dimerization and associated signaling. Disruption of TK activity or the activity of secondary cytoplasmic messengers would inhibit intracellular

signaling.[5] Monoclonal antibodies, TK inhibitors, and multitargeted agents are potent therapeutic weapons to counteract aberrant cellular behavior resulting from abnormal signaling.

Monoclonal Antibodies

The monoclonal antibody (MoAb) has a Y shape with two active sites: the Fab portion (arms of the Y), which recognizes and binds to a specific antigen, and the Fc portion (leg of the Y), which signals the immune system to eliminate the antigen or the associated cell. Each of the four types of MoAbs has a slightly different composition. *Murine MoAbs*, derived from mice, are limited by a short half-life and the potential to create human antimouse antibodies. In an attempt to improve efficacy and the side-effect profile, scientists have engineered MoAbs that contain fewer murine and more human components. Chimeric MoAbs are approximately 75% human; *humanized MoAbs* contain a small murine Fab portion and are 95% to 98% human; and the *fully human MoAbs* contain only the human antibody gene sequence.[6]

The monoclonal antibody primary mechanism of action lies in the extracellular domain and is directed at disrupting ligandreceptor activity. By binding to specific targets, MoAbs disrupt extracellular signaling. A MoAb can bind with a ligand and prevent ligand-receptor pairing, or it can bind with a receptor, inhibiting ligand-dependent receptor activation. A MoAb can also interfere with the activation of ligand-independent receptors. By disrupting ligand-receptor binding, MoAbs prevent phosphorylation and thereby inhibit TK signal transduction pathways. MoAbs have the ability to destroy the cell associated with the antigen by eliciting an effector response from the antibody-dependent cell-mediated cytotoxicity and the complement dependent cytotoxicity systems.[6]

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) are small molecules that can cross the cell membrane and block intracellular signaling. The TKI occupies the ATP binding site on the receptor's intracellular TK domain. Blocking ATP binding prevents phosphorylation and activation of the intracellular signaling cascade. Tyrosine kinase inhibitors are oral agents that demonstrate a common mechanism of action but differ in their specificity, potency, and reversibility.[7]

Multiple Receptor Tyrosine Kinase Inhibitors

Several characteristics of cancer, particularly the signal transduction pathways, support the development of multitargeted therapeutic interventions. Because most cancers develop as a result of multiple mutations in numerous signaling pathways, therapies aimed at simultaneous inhibition of multiple pathways may be more effective than those that inhibit a single pathway. Tumors and their supporting vasculature usually express multiple receptor TKs that regulate key cellular activities such as angiogenesis and proliferation.[7] Signaling cross-talk occurs throughout the signal transduction pathway, enabling one signal to affect the output of another. Targeting multiple receptor TKs may, therefore, elicit a vigorous and rapid biological response. Multitargeted therapeutic agents may not only be more effective than single-target agents but may possibly decrease the occurrence of drug resistance as well. Combining single-target agents has produced an enhanced effect in clinical trials.[8] The US Food and Drug Administration has approved several multitargeted agents in the last year, and many more are in development. The question remains whether treatment is more effective with a combination of single-target agents or with one multitargeted agent. Combining multiple single-target agents would permit flexible dosing, whereas a single multitargeted agent may be more cost-effective and convenient, thereby improving patient compliance.[8]

Indications and Uses of Molecularly Targeted Agents

The FDA has approved nine molecularly targeted agents during the past decade for treatment of cancer patients with solid tumors.[14] Standard clinical practice now includes use of targeted agents

Table 1 : Molecular Targeted Therapy

Cancer	FDA Approved Agent
Breast	Trastuzumab
Colorectal	Bevacizumab
	Cetuximab
	Panitumab
Gastrointestinal stromal tumors	Imatinib
	Sunitinib
Head and neck squamous cell	Cetuximab
Lung / non-small cell	Gefitinib (restricted use only)
	Erlotinib
Pancreatic	Erlotinib
Renal cell	Sorafenib
	Sunitinib

with atleast seven types of solid tumors (Table 1). Clinical trials continue to investigate these drugs and additional agents will be added to the cancer treatment armamentarium in the near future.

Trastuzumab

Mechanism of Action

- Recombinant humanized monoclonal antibody directed against the extracellular domain of the HER-2/neu human epidermal growth factor receptor. This receptor is overexpressed in several human cancers, including 25%-30% of breast cancers.
- Precise mechanism(s) of action remains unknown.
- Down regulates expression of HER-2/neu receptors.
- Inhibits HER-2/neu intracellular signaling pathways.
- Induction of apoptosis through as yet undetermined mechanisms.
- Immunologic mechanisms may also be involved in antitumor activity, and they include recruitment of antibody-dependent cellular cytotoxicity (ADCC) and/or complement-mediated cell analysis.[10]

Dosage Range

- Recommended loading dose of 4 mg/kg IV administered over 90 minutes, followed by maintenance dose of 2 mg/kg IV on a weekly basis
- Alternative schedule is to give a loading dose of 8 mg/kg IV administered over 90 minutes, followed by maintenance dose of 6 mg/kg IV every 3 weeks.

Special Consideration

- Caution should be exercised in treating patients with preexisting cardiac dysfunction. Careful baseline assessment of cardiac function before treatment and frequent monitoring of cardiac function while on therapy. Trastuzumab should be stopped immediately in patients who develop clinically significant congestive heart failure.

Toxicity Profile

Infusion-related symptoms with fever, chills, urticaria, flushing, fatigue, headache, bronchospasm, dyspnea, angioedema and hypotension. Occurs in 40%-50% of patients. Usually mild to moderate in severity and observed most commonly with administration of the first infusion.

Nausea and vomiting, diarrhea. Generally mild.

Cardiotoxicity in the form of dyspnea, peripheral edema, and reduced left ventricular function. Occurs in 5-7% of patients treated with trastuzumab alone, in 25-30% of patients treated with trastuzumab plus anthracycline and in 12% of patients treated with trastuzumab plus paclitaxel. Significantly increased risk when used in combination with an anthracycline/cyclophosphamide regimen. In most instances, cardiac dysfunction is readily reversible.[11]

Myelosuppression. Increased risk and severity when trastuzumab is administered with chemotherapy

Generalized pain, asthenia, and headache

Pulmonary toxicity in the form of increased cough, dyspnea, rhinitis, sinusitis, pulmonary infiltrates, and/or pleural effusions

Indications

As a single agent for the treatment of patients with metastatic breast cancer whose tumors over express the HER2 protein and who have received 1 or more chemotherapy regimens for their metastatic disease. In combination with paclitaxel for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. Neoadjuvant, adjuvant and metastatic breast cancer. In combination with cytotoxic agents other than anthracyclines.[12]

Gefitinib

Mechanism of Action

- Potent and selective small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, resulting in inhibition of EGFR autophosphorylation and inhibition of EGFR signaling.
- Inhibition of the EGFR tyrosine kinase results in inhibition of critical mitogenic and antiapoptotic signals involved in proliferation, growth, metastasis, angiogenesis, and response to chemotherapy and/or radiation therapy.[13]

Metabolism

Metabolism in the liver primarily by the CYP3A4 microsomal enzyme. Other cytochrome P450 enzymes play a minor role in its metabolism. Elimination is mainly hepatic with excretion in the feces, and renal elimination of parent drug and its metabolites account for less than 4% of an administered dose. The terminal half-life of the parent drug is 48 hours.[13]

Indications

- Third line therapy (restricted use) in patient with advanced NSCLC after failure of both platinum and docetaxel based chemotherapy. After 9/15/05 no new patients are allowed access to gefitinib unless they are enrolled in a clinical trial that was approved by an IRB prior to 6/17/05, or they are post to a clinical study being conducted under an investigational new drug application. To be used only in patients who are bending or have benefited from gefitinib.[14]

Dosage Range

- Recommended dose is 250 mg/day PO.

Drug Interaction

- Dilantin and other drugs that stimulate the liver microsomal CYP3A4 enzyme, including carbamazepine, rifampicin, phenobarbital, and St. John's wort - These drugs increase the rate of metabolism of gefitinib resulting in its inactivation.[14]
- Drugs that inhibit the liver microsomal CYP3A4 enzyme, including ketoconazole, itraconazole, erythromycin, and clarithromycin - These drugs decrease the rate of metabolism of gefitinib, resulting in increased drug levels and potentially increased toxicity.[14]
- Warfarin-Patients receiving coumarin-derived anticoagulants should be closely monitored for alterations in their clotting parameters (PT and INR) and/or bleeding as gefitinib inhibits the metabolism of warfarin in the liver P450 system. Dose of warfarin may require careful adjustment in the presence of gefitinib therapy.[14]

Special Considerations[14]

- Clinical responses may be observed within the first week of initiation of therapy.
- Patients with bronchoalveolar non-small cell lung cancer may be more sensitive to gefitinib therapy than other histologic subtypes. Females and non-smokers also show increased sensitivity to gefitinib therapy.
- In patients who develop a skin rash, topical antibiotics and oral minocycline may help.

Toxicity[15]

- Elevations in blood pressure, especially in those with underlying hypertension

- Pruritus, dry skin with mainly a pustular, acneiform skin rash
- Mild to moderate elevations in serum transaminases. Usually transient and clinically asymptomatic
- Asthenia and anorexia
- Mild nausea / vomiting and mucositis
- Conjunctivitis, blepharitis and corneal erosion with abnormal eyelash growth
- Rare episodes of hemoptysis and GI hemorrhage.

Erlotinib

Mechanism of Action

- Potent and selective small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, resulting in inhibition of EGFR autophosphorylation and inhibition of EGFR signaling.
- Inhibition of the EGFR tyrosine kinase results in inhibition of critical mitogenic and antiapoptotic signals involved in proliferation, growth, metastasis, angiogenesis, and response to chemotherapy and/or radiation therapy.[16]

Metabolism

Metabolism in the liver primarily by the CYP3A4 microsomal enzyme and by CYP1A2 to a lesser extent. Elimination is mainly hepatic with excretion in the feces, and renal elimination of parent drug and its metabolites account for about 8% of an administered dose. The terminal half-life of the parent drug is 36 hours.

Dosage Range

- Recommended dose is 150 mg/day P.O.

Special Consideration

- In patients with hepatic impairment, dose reduction or interruption should be considered.
- Non-smokers and patients with EGFR-positive tumors are more sensitive to erlotinib therapy.
- Coagulation parameters PT/INR should be closely monitored when patients are receiving both erlotinib and coumadin, as erlotinib may inhibit the metabolism of coumadin by the liver P450 system.[17, 18]
- In patients who develop a skin rash, topical antibiotics and oral minocyc1ine may help.

Indications

- Monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen. Indicated in combination with gemcitabine for first line treatment of patients with locally advanced, Unresectable or metastatic pancreatic cancer.[17,18]

Cetuximab

Classification

- Monoclonal antibody

Mechanism of Action

- Recombinant humanized monoclonal antibody directed against the epidermal growth factor receptor (EGFR). EGFR is overexpressed in a broad range of human solid tumors, including colorectal cancer, head and neck cancer, non-small cell lung cancer, pancreatic cancer, and breast cancer.[19]
- Precise mechanism(s) of action remains unknown.
- Binds with nearly 10-fold higher affinity to EGFR than normal ligands EGF and TGF-a, which then results in inhibition of EGFR. Prevents both homodimerization and heterodimerization of the EGFR which then leads to inhibition of autophosphorylation and inhibition of EGFR signaling.[20]
- Inhibition of the EGFR signaling pathway results in inhibition of critical mitogenic and anti-apoptotic signals involved in proliferation, growth, invasion/metastasis, angiogenesis,
- Inhibition of the EGFR pathway enhances the

response to chemotherapy and/or radiation therapy.

- Immunologic mechanisms may also be involved in antitumor activity, and they include recruitment of antibody-dependent cellular cytotoxicity (ADCC) and/or complement-mediated cell lysis.[20]

Indications

- Treatment of patients with metastatic colorectal cancer whose tumor expresses the EGFR protein. Treatment is given either in combination with irinotecon for patients refractory to irinotecon, or as a single agent for those unable to tolerate chemotherapy with irinotecan.[21]
- Indicated in combination with radiotherapy for the treatment of locally or regionally advanced squamous cell head and neck cancer. Cetuximab alone is indicated for the treatment of the patients with squamous head and neck cancer whose tumor has progressed or metastatic after treatment with platinum based therapy.[22,23]
- Unresectable loco-regional recurrence or second primary in patients with squamous cell head and neck cancers who have received prior radiotherapy.[24,25]

Metabolism

- Metabolism of cetuximab has not been extensively characterized. Half life is on the order of 5-7 days with minimal clearance by the liver or kidneys.

Dosage Range

- Loading dose of 400 mg/m^2 IV administered over 90 minutes, followed by maintenance dose of 250 mg/m^2 IV given on a weekly basis.

Special Considerations

- Cetuximab should be used with caution in patients with known hypersensitivity to murine proteins and/ or any individual components.
- There is no scientific or clinical evidence to suggest that the level EGFR expression can accurately predict for cetuximab clinical activity. The clinical activity of Cetuximab is the same in EGFR-positive and EGFR-negative colorectal cancer.
- Development of skin toxicity appears to be a surrogate marker for Cetuximab clinical activity.
- In patients who develop a skin rash, antibiotic such as oral minocycline may help. Topical steroids and/or oral steroid treatment do not appear to be helpful in this setting. Patients should be warned to avoid sunlight exposure.

Toxicity[20]

- Infusion-related symptoms with fever, chills, urticaria, flushing, fatigue, headache, bronchospasm, dyspnea, angioedema, and hypotension. Although severe reactions occur in less than 1%. Usually mild to moderate in severity and observed most commonly with administration of the first infusion.
- Pruritus, dry skin with mainly a pustular, acneiform skin rash. Presents mainly on the face and upper trunk. Improves with continued treatment and resolves upon cessation of therapy.
- Pulmonary toxicity in the form of interstitial lung disease (ILD) manifested by increased cough, dyspnea, and pulmonary infiltrates. Observed in less than 1% of patients and more frequent in patients with underlying pulmonary disease
- Hypomagnesemia.
- Asthenia and generalized malaise observed in nearly 50% of patients.
- Paronychial inflammation with swelling of the lateral nail folds of the toes and fingers.

Sunitinib Malate

Mechanism of Action

Sunitinib is an oral, multitargeted RTK inhibitor of vascular endothelial growth factor receptor

(VEGFR)-1, -2 and -3, platelet-derived growth factor receptor (PDGFR) -α and -β, as well as other RTKs including stem cell factor receptor (KIT), glial cell line-derived neurotrophic factor and FMS-like receptor tyrosine kinase (FLT3).[26]

Indications

Sunitinib was approved in 2006 by the European Medicines Agency (EMEA) for use in advanced and/or metastatic RCC and by the United States Food and Drug Administration (FDA) for the treatment of **advanced RCC**. At the same time, sunitinib was approved by the EMEA for use in unresectable and/or metastatic **malignant gastrointestinal stromal tumour (GIST)** after failure of imatinib treatment due to resistance or intolerance and by USA FDA for the treatment of GIST after disease progression on or intolerance to imatinib mesylate treatment. The efficacy of sunitinib has been demonstrated in two independent, single-arm, multi center, phase II studies (trial 1: n = 63; trial 2: n = 106) in patients with cytokine-refractory metastasis RCC.[27,28] On the basis of the favourable phase II efficacy and safety data, a multi center, randomized phase III study compared sunitinib with IFN-Iα as first-line therapy in metastatic RCC.[27] Sunitinib has recently received European Union approval as first-line treatment for advanced and/or metastatic RCC.

Dosage

Sunitinib was administered at a dose of 50 mg/day, on a 4 weeks on then followed by 2 weeks off schedule. Patients continued on sunitinib unless there was disease progression or treatment intolerance.

Toxicity

Treatment with sunitinib was generally well tolerated. The tolerability profile of sunitinib was similar across the trials. The majority of adverse events reported were manageable with temporary delays, dose reduction and/or standard medical interventions. Dose reductions were required by approximately one-third and one-quarter of patients in trials 1 and 2, respectively. The most commonly reported grade 3, nonhematological treatment-related adverse events included fatigue (11% in both trials) and hand-foot syndrome (7% in trial 2). No non-hematological adverse events were experienced at grade 4 severity.[26,27,28]

Sorafenib Tosylate

Mechanism of Action

Sorafenib is an oral, multi targeted kinase inhibitor. The molecular targets of sorafenib include the tyrosine kinases VEGFR-2 and-3, PDGFR-β, FLT3, KIT and RET, and the serine threonine Raf kinases, B-Raf and Raf-1/C-Raf. Sorafenib received approval from EMEA in July 2006 for the treatment of advanced RCC after failure of prior cytokine therapy or for patients who would be unsuitable for such therapy. FDA approval was granted in December 2005 for the treatment of patients with advanced RCC.[29]

Indications

The efficacy of sorafenib in the second-line setting was initially seen in a phase II randomized discontinuation trial.[30] Results from the randomized discontinuation study then led to an international phase III randomized controlled study of sorafenib versus placebo in patients with previously treated RCC. In this 'Treatment Approaches in Renal cell cancer Global Evaluation Trial' (TARGET trial), patients with **unresectable or metastatic RCC** were randomized to sorafenib 400 mg twice daily or placebo.[31] After the first interim analysis of OS, which showed that sorafenib reduced the risk of death as compared with placebo patients were allowed to crossover from placebo to sorafenib. Of 451 patients receiving sorafenib and who were assessable for investigator-assessed response, 10% achieved a PR, and 74% had SD compared with 2% and 53%, respectively, in the placebo-treated arm ($n = 452$).[31] Adverse events were similar in phase II and III studies.

Side Effects

The most commonly reported grade 3/4 adverse

events included fatigue and hypertension. Diarrhea (43% Vs 13%); rash or desquamation (40% Vs 16%); fatigue (37% Vs 28%) and hand-foot skin reactions (30% Vs 7%).[31]

Special Considerations

These results confirm that targeted inhibition of these single and multiple tumor targets is a feasible approach to treatment and provides a more positive outlook for the future management of metastatic RCC. Given the clinical experience with these agents in the metastatic setting, their role as adjuvant treatment is now being explored in a number of large-scale randomized trials in patients at risk of relapse following surgery. In addition to multitargeted RTK inhibitors, other targets being investigated include hypoxia-inducible factor and intracellular signal transduction targets involved in proliferation, survival and hypoxia stimulation.[32]

Bevacizumab

Mechanism of Action

- Recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF). Binds to all isoforms at VEGF-A. VEGF is a pro-angiogenic growth factor that is overexpressed in a wide range of solid human cancers, including colorectal cancer.
- Precise mechanism(s) of action remains unknown.
- Binding of VEGF prevents its subsequent interaction with VEGFR receptors on the surface of endothelial cells and tumors, and in so doing, results in inhibition of VEGFR-signaling.
- Inhibits formation of new blood vessels in primary tumor and metastatic *tumors*.
- Restores antitumor response by enhancing dendritic cell function.
- Immunologic mechanisms may also be involved in antitumor activity, and they include recruitment of antibody-dependent cellular cytotoxicity (ADCC) and/or complement-mediated cell lysis.[33]

Metabolism

- Metabolism of bevacizumab has not been extensively characterized. Half-life is on the order of 17-21 days with minimal clearance by the liver or kidneys, as has been observed for other monoclonal antibodies and peptides used in the clinic.

Dosage Range

- Recommended dose for the treatment of colorectal cancer is 5 mg/kg IV on an every two week schedule.
- Can also be administered at 7.5 mg/kg IV every 3 weeks when used in combination with capecitabine-based regimens.

Special Considerations

- Patients should be warned of the increased risk of arterial thromboembolic events, including myocardial infarction and stroke. Risk factors are age $>$ 65 years and history of angina, stroke, and prior arterial thromboembolic events.
- In some cases, fatal hemorrhage resulting from hemoptysis in patients with non-small cell lung cancer. These events have been mainly observed in patients with a central, cavitary, and/ or necrotic lesion involving the pulmonary vasculature.
- Bevacizumab treatment can result in the development of gastrointestinal perforations and wound dehiscence, which in some cases, has resulted in death.
- Use with caution in patients with uncontrolled hypertension as bevacizumab can result in grade 3 hypertension in about 10% of patients.

Toxicity

- Gastrointestinal perforations and wound healing complications.
- Bleeding complications with epistaxis being most commonly observed.
- Increased risk of arterial thromboembolic

events, including myocardial infarction, angina, and stroke.

- Hypertension occurs in up to 20-30% of patients with grade 3 hypertension observed in 10-15% of patients. Usually well-controlled with oral anti-hypertensive medication.
- Proteinuria with nephrotic syndrome developing in up to 5% of patients.
- Infusion-related symptoms with fever, chills, urticaria, flushing, fatigue, headache, bronchospasm, dyspnea, angioedema, and hypotension. Relatively uncommon event occurring in less than 5% of patients.[33]

Indications

- In combination with IV 5-FU-based chemotherapy is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.[34]
- In combination with IV 5-FU-based chemotherapy for second-line treatment of metastatic cancer or colon or rectum.
- Recommendations (NCCN 2006 Guidelines) available for advanced NSCLC, loco-regional and metastatic breast cancer, renal cell carcinoma, Neoadjuvant and adjuvant colorectal carcinoma, recurrent ovarian cancer.[34,35,36]

Investigational Agents

Lapatinib

Targeting the HER family of TKs remains an intriguing prospect for the treatment of solid tumors. Preclinical and clinical investigations of lapatinib, are under way. Lapatinib is a HER-family targeted therapy. Lapatinib is an oral agent that acts as a dual TKI in the intracellular domain. While all EGFR-inhibiting agents have been designed for single targets, lapatinib has the novel mechanism of targeting both HER1 and HER2. Lapatinib is available for use only in clinical trials involving patients with a variety of solid tumors. Early results for the treatment of advanced breast cancer are encouraging.[37]

Conclusion

Molecularly targeted therapies are becoming a mainstay of treatment for cancer patients. By learning the science and applications of these therapies, oncologists can improve their own knowledge base and enhance the treatment response outcomes in patients at a significantly reduced morbidity and mortality, even in advanced stages of disease. This translates into greater survival with a much better quality of life quotient in the patient population.

References

1. Perez-Soler R: HER1/EGFR targeting: Refining the strategy. Oncologist 2004. 9:58-67.
2. Lenz HJ: Anti-EGFR mechanism of action: Antitumor effect and underlying cause of adverse events. *Oncology* 2006. 20:5-12.
3. Yarden Y, Baselga J, Miles 0: Molecular approach to breast cancer treatment. *Semin Oncol* 2004. 31:6-13.
4. Farrara N: Vascular endothelial growth factor as a target for anticancer therapy. *Oncologist* 2004. 9(suppl1):2-10.
5. Adjei A, Hidalgo M: Intracellular si9nal transduction pathway proteins as targets for cancer therapy. *J Clin Oncol* 2005. 23:5326-5403.
6. Cheifetz A, Mayer L: Monoclonal antibodies, immunogenicity, and associated infusion reactions. *Mt Sinai J Med* 2005. 72:250-259.
7. Patyna S, Laird AD, Mendel DB, et al: SU 14813: A novel multiple receptor tyrosine kinase inhibitor with potent antiangiogenic and antitumor activity. *Mol Cancer Ther* 2006. 5:1774 -1782.
8. Sandler A, Herbst R: Combining targeted agents: Blocking the epidermal growth factor and vascular endothelial growth factor pathways. *Clin Cancer Res* 2006. 12:4421s-4425s.
9. McNeil C: Two targets, one drug for new EGFR inhibitors. *NJCI* 2006. 98: 1103-1104.
10. Herceptin (trastuzumab) package insert. Genentech, Inc, San Francisco, CA: February 2005.
11. Jackisch C: HER2-positive metastatic breast cancer optimizing trastuzumab-based therapy. *Oncologist* 2006. 11(suppl1): 34-41.
12. Baselga J, Perez E, Pienkowski T, et al: Adjuvant trastuzumab: A milestone in the treatment of HER2-positive early breast cancer. *Oncologist* 2006. 11(suppl1):4-12.
13. Iressa (gefitlnib) tablets, package inserts. AstraZeneca Pharmaceuticals, Wilmington, DE: June 2005.
14. US Food and Drug Administration: Catalog of approved cancer drugs. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction = Search. Label Approval History # apphist Iressa. Accessed

August 15. 2006.

15. US Food and Drug Administration: Safety alerts for drugs, biologics, medical devices, and dietary supplements. Available at http://www.fda.gov/cder/drug/infopage/ gefitinib/default. htm 2005 Iressa. Accessed September 9, 2006.

16. Tarceva (erlotinib) tablets, package insert, Genentech, San Francisco, CA. and OSI Oncology, Melville, NY: November; 2005.

17. Shepard FA, Pereira JR, Ciuleanu T, et al, for the National Cancer Institute of Canada Trials Group: Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005. 353:123-132.

18. Tsao MS, Sakurada A, Cutz JC, et al: Erlotinib in lung cancer-Molecular and clinical predictors of outcome. *N Engl J Med* 2005. 353'133-144.

19. Vokes EE, Chu E: Anti-EGFR therapies: Clinical experience in colorectal, lung and head and neck cancer. *Oncology* 2006. 20(suppl 2): 17-25.

20. Erbitux (cetuximab) package insert. ImClone Systems Inc, Branchberg, NJ, and Bristol Myers Squibb'Co, Princeton, NJ: March 2006.

21. Cunningham D, Humblet Y, Siena S. et al: Cetuximab monotherapy and cextuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004. 351:337-345.

22. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006. 354:567 -578.

23. Trigo J, Hit R, Koralewski P, et al: Cetuximab monotherapy is active in patients (pts) with platinum refractory recurrent/ metastatic squamous cell carcinoma of the head and neck (SCCHN): Results of a phase II study (abstract 5502) [and slide presentation]. Proc Am Soc Clin Oncol 2004 23:487.

24. Baselga J, Trigo JM, Bourhis J, et al: Phase II multicenter study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2005. 23:5578-5587.

25. Herbst RS, Shin OM, Dicke K, et al: Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory head and neck. *J Clin Oncol* 2005. 23:5568-5577.

26. Sutent (sunitinib malate) package insert. Pfizer Lbs, New York, February 2006.

27. Mortez RJ, Michaelson MD, Redman BG et al. Activity of SU11248, a multitrageted inhibitors of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J. Clin. Oncol* 2006; 24: 16-24

28. Mortez RJ, Rini BL, Bukowski RM et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006; 2516 – 2524

29. Nexavar (sorafenib) package insert. Bayer Pharmaceuticals Corp, West Haven, CT: August 2006.

30. ratain MJ, Eisen T, Stadler WM et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with Metastatic renal cell carcinoma. *J Clin Oncol* 2006; 24: 2505 – 2512

31. Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear cell renal cell carcinoma. *N Engl J Med* 2007; 356: 125 – 134

32. Schoffski P, Dumez H, Clement P et al. Emerging role of tyrosine kinase inhibitors in the treatment of advanced renal cell cancer : a review. *Ann Oncol* 2006; 17: 1185 – 1196

33. Avastin (bevaclzumab) package Insert. Genentech, San Francisco, CA, June 2006.

34. Benson AB, Catalano PJ, Meropol J, et al: Bevacizumab (anti-VEGF) plus FOLFOX 4 in previously treated advanced colorectal cancer (adv CRC): An interim toxicity analysis of the Eastern Cooperative Group (ECOG) study E3200 (abstract 975). Proc Am Soc Clin Oncol 2003. 22:243.

35. Miller K, Wang M, Gralow J, et al: E2100, a randomized phase III trial of paclitaxel vs. paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. [Presentation]. American Society of Clinical Oncology 41st annual meeting, Orlando, Florida, Z005.

36. NCCN Clinical Practice Guidelines in Oncology: Available at www.nccn.org. Accessed September 19, 2006.

37. Geyer CE, Forster JK, Cameron OS: Phase III randomized, open-label, international study comparing lapatinib and capecitabine versus capecitabine in women with refractory advarlced or metastatic breast cancer. American Society of clinical Oncology 42nd annual meeting, Atlanta, 2006.