17 Monoclonal Antibodies in Cancer

Amy Grimsley, Katherine S. Shah, and Trevor McKibbin

INTRODUCTION

Cancer is the second leading cause of death in the United States with one of every four deaths attributable to cancer (Jemal et al. 2006). The first references to cancer date back to Egyptian papyrus circa 1600 BC. The introduction of nitrogen mustards in the 1940s can be considered the origin of modern, systemic antineoplastic therapies (Papac 2001). Rapid improvements in the understanding of cancer biology, medicinal chemistry, and biopharmaceutical technology have provided rationally designed drugs exploiting differences in normal and malignant cells. Monoclonal antibodies (MABs) bind to a specific epitope. This allows for a targeting approach for the development of effective anticancer compounds with relatively less and/or nonoverlapping toxicity compared to other cytotoxic drugs used to treat cancer. In cancer treatment, MABs have been developed that exert a wide array of pharmacologic effects. This chapter focuses on FDA-approved MABs for the treatment of cancer and cancer-related symptoms. Antibodies are organized based on their target. Table 17.1 summarizes the current FDA-approved MABs for cancer indications, year of approval, target, and the indications that are discussed within the chapter.

A. Grimsley, PharmD
Department of Pharmacy Practice,
Mercer University College of
Pharmacy and Health Sciences,
Atlanta, GA, USA

K.S. Shah, PharmD • T. McKibbin, PharmD, MS, BCPS (✉)
Department of Pharmaceutical Services,
Emory University Hospital/Winship Cancer Institute,
1365 Clifton RD, Building C,
Atlanta 30322, GA, USA
e-mail: trevor.mckibbin@emory.edu

CLASSES OF MONOCLONAL ANTIBODIES: CD ANTIGENS

■ Alemtuzumab

Pharmacology and Pharmacokinetics

Alemtuzumab is an unconjugated, humanized, IgG_1 kappa MAB directed against the 21–28 kDa cell surface glycoprotein CD52 (Frampton and Wagstaff 2003). Most lymphocytes (including 95 % of B and T cells at various stages of differentiation), monocytes, natural killer cells, macrophages, and eosinophils, as well as cells lining the male reproductive tract, express CD52; however, it is not found on erythrocytes, platelets, or stem cells (Liu and O'Brien 2004). While CD52 is highly expressed in some forms of chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), and acute lymphoblastic leukemia (ALL), it is not shed or internalized, making it an ideal therapeutic target (Liu and O'Brien 2004). Malignant CD52 expression occurs not only in CLL, low-grade lymphomas, and T-cell malignancies but also in some cases of myeloid, monocytic, and acute lymphoblastic leukemias. The compound exerts its anticancer effects by binding to CD52 antigenic sites and stimulating cross-linking by antibodies, which promotes antibody-dependent cellular cytotoxicity and direct cellular apoptosis via natural killer activity as shown in Fig. 17.1 (O'Brien et al. 2005).

Pharmacokinetic parameters of alemtuzumab were determined in a phase I dose-escalation trial. Patients with B-cell CLL and NHL were given alemtuzumab intravenously once weekly for a maximum of 12 weeks, and plasma levels were obtained (Frampton and Wagstaff 2003). A dose-proportional increase in maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC) was observed. The median half-life ($t_{1/2}$) was approximately 12 days. A subsequent pharmacokinetic analysis was conducted in CLL patients who received alemtuzumab 30 mg intravenously three times weekly. A high degree of interpatient

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Generic name	Approval year	Origin	Target	Indications
Cluster of differentiation (CD) targeted				
Alemtuzumab	2001	Humanized	CD-52	B-cell CLL
Gemtuzumab	2000[a]	Humanized	CD-33	AML –compassionate use program only
Rituximab	1997	Chimeric	CD-20	Non-Hodgkin's lymphoma
Yttrium-90 (^{90}Y) ibritumomab tiuxetan	2002	Murine	CD-20	B-cell non-Hodgkin's lymphoma
Iodine-131 (^{131}I) tositumomab	2003	Murine	CD-20	Non-Hodgkin's lymphoma
Brentuximab vedotin	2011	Chimeric	CD-30	Hodgkin's lymphoma
Ofatumumab	2009	Human	CD-20	CLL
Epidermal growth factor receptor (EGFR) targeted				
Cetuximab	2004	Chimeric	EGFR	Colorectal cancer, SCCHN
Panitumumab	2006	Human	EGFR	Colorectal cancer
Trastuzumab	1998	Humanized	HER2/neu	Breast cancer, gastric cancer
Vascular endothelial growth factor (VEGF) targeted				
Bevacizumab	2004	Humanized	VEGF	NSCLC, colorectal cancer, glioblastoma multiforme, metastatic renal cell carcinoma
Receptor activator of nuclear factor kappa B ligand (RANKL)				
Denosumab	2010	Human	RANKL	Cancer metastatic to the bone
Cytotoxic T-lymphocyte antigen-4 (CTLA-4)				
Ipilimumab	2011	Human	CTLA-4	Metastatic melanoma

CLL chronic lymphocytic leukemia, *AML* acute myeloid leukemia, *VEGF* vascular endothelial growth factor, *NSCLC* non-small cell lung cancer, *EGFR* endothelial growth factor receptor, *SCCHN* squamous cell carcinoma of the head and neck
[a]Approval subsequently denied.

Table 17.1 ■ FDA-approved monoclonal antibodies in cancer.

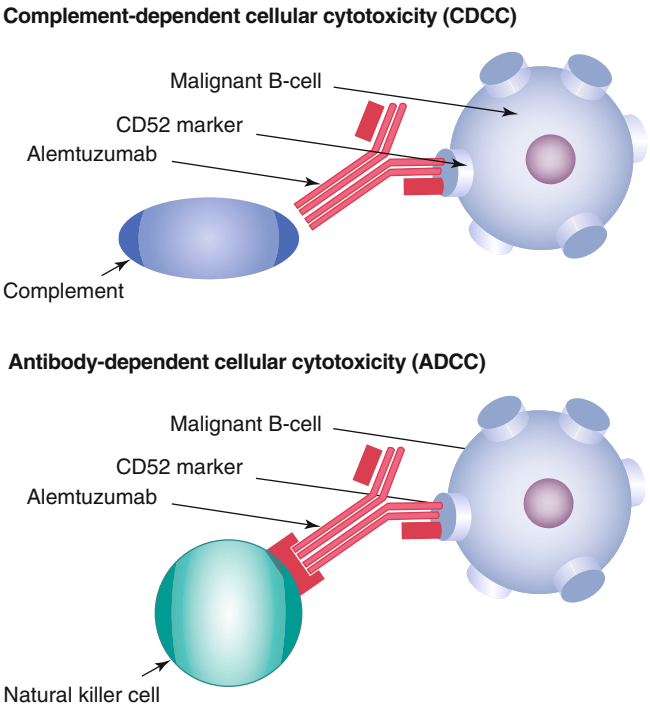

Figure 17.1 ■ Alemtuzumab mechanism of action. Diagram showing alemtuzumab bound to the CD52 surface marker on chronic lymphocytic leukemia cells where it triggers complement-dependent cytotoxicity and natural killer cell action (*Source*: The Association of the British Pharmaceutical Industry).

variability was observed and patients exhibited a trend of gradually rising plasma concentrations during initial therapy, which continued until steady state was achieved. This typically occurred after 6 weeks. Authors noted that the rise in alemtuzumab concentrations corresponded to a simultaneous decline in circulating CD52-positive malignant lymphocytes.

Alemtuzumab has also been given subcutaneously (Montagna et al. 2011). In one comparative study, 29 patients with relapsed CLL received intravenous alemtuzumab 30 mg thrice weekly, while 20 patients received the same dose subcutaneously. The authors noted that over time, maximal trough concentrations progressed to similar levels in both groups; however, accumulation of antibody in the blood was slower in the subcutaneous group, with these patients requiring slightly higher cumulative doses to achieve similar concentrations (Montagna et al. 2011). In this study, the mean steady-state volume of distribution (Vd) among both groups of patients during initial treatment was 0.185 L/kg, which expanded to 0.252 L/kg during the terminal phase. The large Vd is consistent with the notion that alemtuzumab distributes beyond the plasma compartment to an extravascular lymphocytic compartment. Mean

terminal half-life was 6.1 days in this population and clearance appeared to correlate with antigenic burden (Dirks and Meibohm 2010). Patients with undetectable CLL cells exhibited a single elimination phase with a longer half-life, whereas patients with bulkier tumors cleared alemtuzumab more rapidly. The most dominant factor influencing alemtuzumab pharmacokinetic parameters appears to be CD52 concentration, which accounts for much of the interpatient variability.

Indications and Clinical Efficacy

While it is utilized in a variety of disease states including many T-cell malignancies, alemtuzumab is FDA approved for use in B-cell CLL patients who have been treated with alkylating agents and failed fludarabine therapy. Alemtuzumab was commercially available under the branded name Campath® for the treatment of leukemias until September 2012. Given recent encouraging results in phase III studies in Multiple Sclerosis the manufacturer has removed Campath® from the market to prevent unauthorized use. Though Campath is available free of charge for the treatment of malignancy, alemtuzumab is being re-branded to Lemtrada™ for the treatment of Multiple Sclerosis. Three major studies have assessed alemtuzumab in this population (Keating and Hallek 2002; Rai et al. 2002; Osterborg et al. 2002). An international collaboration of centers in the United States and Europe published the largest of these studies. Ninety-two fludarabine-resistant patients, of whom 76 % had Rai stage III or IV disease, were treated with 12 weeks of intravenous alemtuzumab (Keating and Hallek 2002). The overall response rate was 33 %, with 2 % achieving a complete response (CR). Median survival was 16 months. Patients with bulky lymphadenopathy were less likely to respond, possibly indicating poor tumor penetration of alemtuzumab (Keating and Hallek 2002; Liu and O'Brien 2004). Toxicity was moderate and consisted mainly of infections and infusion reactions. A study evaluating alemtuzumab treatment in 24 poor-prognosis, fludarabine-resistant chronic lymphocytic leukemia patients confirmed these findings (Rai et al. 2002). After approximately 16 weeks of treatment with alemtuzumab (target dose 30 mg three times weekly), the overall response rate was 33 % and the median time to progression was 19.6 months.

Because of the high incidence of infusion-related reactions encountered with alemtuzumab intravenous infusion, subcutaneous administration has been explored as a potential alternative. A pivotal trial evaluated subcutaneous alemtuzumab as first-line therapy in 41 patients with advanced, previously untreated CLL (Lundin et al. 2002). The subcutaneous alemtuzumab resulted in an overall response rate of 87 %, with 19 % CR. While injection site reactions were seen in 90 % of patients, these were grades 1–2 in severity and typically disappeared with continued treatment (often within 2 weeks). The more severe infusion reactions encountered with intravenous dosing, such as dyspnea, hypotension, and nausea, were absent; however, some patients did experience fever and rigors (Lundin et al. 2002).

Combination therapy with alemtuzumab has been investigated; one study evaluated six patients with refractory disease who were treated with fludarabine and alemtuzumab concurrently (Kennedy and Hillmen 2002). Five patients responded, with one patient achieving a complete response. Another combination that has been explored is alemtuzumab with rituximab (Faderl et al. 2003; Nabhan et al. 2004). Nabhan and colleagues administered rituximab 375 mg/m^2 weekly for four cycles, adding alemtuzumab thrice weekly on weeks 2–5 in 12 patients with relapsed CLL. One patient achieved a partial response (PR), while 90 % of patients had stable disease. Therapy was relatively well tolerated, with no treatment-related deaths; however, 75 % of patients experienced grade 2 rigors and 33 % exhibited grade 3/4 fevers. A second trial evaluating the combination of rituximab and alemtuzumab used a similar schedule in 48 relapsed CLL and PLL patients. Response rates were strong, with 65 % achieving a PR. However, infection was common, occurring in 56 % of patients (Nabhan et al. 2004). Longer follow-up and additional studies will help to fully elucidate the role of combination therapy with alemtuzumab, further addressing the issue of additive myelosuppression and infectious risk with this agent. Selected clinical studies of alemtuzumab are summarized in Table 17.2.

Safety

The most common adverse effects associated with alemtuzumab, which are also listed as black box warnings, are infusion-related reactions, infectious complications, and hematologic toxicities. Infusion reactions are common and are reported in approximately 90 % of patients (Keating and Hallek 2002; Stilgenbauer et al. 2009). Rigors, fever, nausea, vomiting, and rash are often seen with initial infusions; however, these typically decrease with subsequent drug exposure. Rarely, hypotension and dyspnea are encountered (Liu and O'Brien 2004). Premedication with antihistamines is recommended to reduce this possibility. Subcutaneous administration of alemtuzumab also significantly lessens the risk of infusion-related adverse reactions (Montillo et al. 2006; Stilgenbauer et al. 2009). Subcutaneous administration may also be associated with transient local skin reactions. Another substantial adverse effect commonly associated with alemtuzumab is infection; lymphocyte counts decrease rapidly after treatment,

Investigators	Disease(s), number of patients	Alemtuzumab dosing regimen	CR/PR (%)	Median overall survival	Significant adverse events (grade 3/4)
	Relapsed/refractory B-cell CLL, *n*=93	3 mg IV until tolerated, then 10 mg IV until tolerated, then 30 mg IV thrice weekly for up to 12 weeks	CR 2 PR 31	16 months	Infection 26.9 %
	B- or T-cell CLL after failing fludarabine, *n*=24	10 mg IV until tolerated, then 30 mg IV thrice weekly for up to 16 weeks	PR 33	35.8 months	Neutropenia 20.8 % Infection 41.7 %
	Relapsed/refractory CLL, *n*=29	3 mg IV escalated as tolerated to 30 mg IV thrice weekly for up to 12 weeks	CR 4 PR 38	*Median response duration*=12 months	Neutropenia 41 % Thrombocytopenia 27 % Hypotension 3 % Infection 17 %
Lundin et al. (2002)	Primary B-cell CLL, *n*=41	3 mg SC escalated to 10 mg SC and 30 mg SC as tolerated; then, 30 mg SC thrice weekly for 18 weeks maximum	CR 19 PR 68	Not reached yet; 8–44+ months	Neutropenia 21 % Pain at injection site 7 % Thrombocytopenia 5 % Infection 12 %
Pawson et al. (1997)	Relapsed T-cell PLL, *n*=15	10 mg IV escalated to 30 mg IV thrice weekly as tolerated[a]	CR 60 PR 13	Not reached yet	Hematologic 27 % Infection 33 %
	Relapsed lymphoproliferative disorders, including CLL and T-cell PLL; *n*=78	3 mg IV escalated to 10 mg IV and 30 mg IV as tolerated; then 30 mg IV thrice weekly for 12 weeks maximum	CR 13 PR 22	12 months	Neutropenia 27 % Thrombocytopenia 32 % Dyspnea 7 %
	Relapsed/refractory CLL or PLL, *n*=23	3 mg IV escalated to 10 mg IV and 30 mg IV as tolerated; then 30 mg IV thrice weekly for 12 weeks maximum	CR 35 PR 18	N/A	Neutropenia 9 % Thrombocytopenia 9 % Infection 9 %

CR complete response, *PR* partial response
[a]One patient received subcutaneous alemtuzumab

Table 17.2 ■ Selected clinical trials with alemtuzumab (Campath-1H).

resulting in a severe and extended durations of lymphopenia. This profound T-cell depletion leads to an increased risk of opportunistic infections, particularly CMV reactivation. Additionally, *Herpes simplex* virus infection, *Pneumocystis carinii* pneumonia, candidiasis, and septicemia have all been reported (Keating and Hallek 2002). These commonly manifest between 3 and 8 weeks from treatment, during the nadir of the T-lymphocyte count. It is recommended to assess CD4+ counts after beginning treatment and until ≥200 cells/μL. Prolonged prophylaxis with antibacterial and antiviral medications is highly encouraged. Myelosuppression, on the other hand, consisting of anemia, neutropenia, and thrombocytopenia, tends to be moderate and transient, with grade 4 neutropenia occurring in about 20 % of cases (Keating and Hallek 2002; Kennedy and Hillmen 2002; Liu and O'Brien 2004). A complete blood count should be monitored at least weekly. Dosage modifications for alemtuzumab are recommended for cases of severe myelosuppression.

In rare instances, cardiac toxicity has been reported with alemtuzumab, consisting of atrial fibrillation and left ventricular dysfunction (Lenihan et al. 2004). These case reports have occurred in patients with mycosis fungoides/Sezary syndrome, and authors suggested that patients with T-cell malignancies may be at increased risk of cardiac toxicity from alemtuzumab. However, other reports have found no link between alemtuzumab and cardiac toxicity in patients with mycosis fungoides/Sezary syndrome (Lundin et al. 2005).

Alemtuzumab treatment should be administered according to a dose-escalation schedule. If infusion-related toxicities are ≤ grade 2, the patient may proceed on to the next dose. An initial dose of 3 mg should be given as a 2-h IV infusion daily; if this initial dose is tolerated, the dose should be increased to 10 mg IV

over 2 h; if the 10 mg dose is tolerated, the maintenance dose of 30 mg IV over 2 h may be initiated. Patients receiving alemtuzumab subcutaneously follow this same dose-escalation schema. To help prevent infusion reactions, each dose is preceded by a dose of acetaminophen and an antihistamine. Corticosteroids and other supportive care measures may be administered if severe infusion-related events occur.

■ Gemtuzumab

Pharmacology and Pharmacokinetics

Gemtuzumab ozogamicin (GO) was one of the first commercially available bispecific monoclonal antibodies. This recombinant, humanized, IgG_4 MAB to cell surface marker CD33 is covalently bonded by a bifunctional linker to the potent cytotoxic antibiotic, calicheamicin. Immature and mature myeloid cells, as well as erythroid, megakaryocytic, and multipotent progenitor cells, express the 67-kDa glycosylated transmembrane protein CD33. In addition, this protein is expressed on the surface of most leukemic blast cells found in acute myelogenous leukemia (AML) as well as myelodysplastic syndromes (MDS) (van Der Velden et al. 2001). However, CD33 is not expressed on stem cells, nor is it expressed outside of the hematopoietic system, making it an excellent therapeutic target. The cytotoxic antibiotic calicheamicin is a natural antineoplastic compound derived from *Micromonospora echinospora*. It is made up of two molecules of the enediyne antitumor antibiotic n-acetyl-γ-calicheamicin dimethyl hydrazine (Sievers et al. 1999). This compound, along with its metabolites, has antineoplastic activity that is 1,000 times more potent than doxorubicin (Giles et al. 2003).

GO exerts its clinical effects through direct binding to the CD33 antigen. Following a 9 mg/m^2 dose, CD33 antigenic sites are maximally saturated within 3 h (van Der Velden et al. 2001). Endocytosis quickly follows, resulting in rapid internalization of the antibody-antigen complex. Additional expression of new CD33 antigenic sites occurs after internalization of the GO molecule, leading to further accumulation and increased concentration of intracellular GO. Once inside the cell, GO is directed to lysosomes which cleave the molecule via acid hydrolysis, liberating the calicheamicin compound. Calicheamicin then binds to double-stranded DNA helixes in the minor groove, causing site-specific double strand cleavage at oligopyrimidine-oligopurine tracts. Induction of apoptosis is observed after approximately 72–96 h. In addition to direct induction of apoptosis from calicheamicin, antibody-dependent cell-mediated cytotoxicity and complement-mediated cytotoxicity also stimulate leukemic cell death.

Clinical studies investigating the pharmacokinetic parameters of GO have been conducted in adults with AML in first relapse (Dowell et al. 2001, Korth-Bradley et al. 2001). Initial phase I pharmacokinetic trials found that a dose of 9 mg/m^2 fully saturated CD33 sites in all patients regardless of disease burden. Phase II studies confirmed the efficacy of GO in refractory AML patients and helped consolidate the treatment schedule of two 9 mg/m^2 infusions separated by approximately 14 days. Measurements of serial plasma concentrations have confirmed a distinct difference in pharmacokinetic parameters between the first and second doses, largely thought to be due to a decline in circulating leukemic blast cells that express CD33. A study conducted by Dowell and colleagues in 59 adult patients with relapsed AML found that maximum plasma concentrations (C_{max}) of both MABs and calicheamicin typically occurred shortly after the end of the 2-h infusion; additionally, C_{max} values were generally higher after the second dose (Dowell et al. 2001). Values for volume of distribution changed as well, averaging approximately 20.9 L after the first dose and only 9.9 L after the second. This decrease in Vd is likely also due to a decline in the number of circulating cells expressing CD33. In addition, the relatively low distribution volumes suggest that GO does not distribute beyond the plasma compartment, but rather remains bound to CD33 antigenic sites within the vascular space. This has been confirmed by radiolabeled studies that demonstrate that organs with a large blood pool, such as the spleen and liver, are primarily responsible for uptake and distribution of the antibody. Another pharmacokinetic evaluation of GO by Korth-Bradley and colleagues (2001) compared the kinetic parameters of GO in different populations. Although a great deal of interpatient variability was observed, the authors concluded that there were no significant differences in C_{max}, time to C_{max}, AUC, clearance, or Vd between males and females, nor were there any significant differences between those over 60 and those under 60 years of age. Clearance of GO from the plasma occurs mainly through uptake by CD33-positive cells and subsequent internalization and is therefore influenced by antigen concentration. Elimination half-life of the drug is fairly long and increases upon second exposure. Median half-life of the antibody component is 72.4 h after the first dose and 93.7 h after the second, while the median half-life of the calicheamicin component is 45.1 h after the first dose and 61.1 h after the second (Dowell et al. 2001a). Accumulation between doses was not found to be significant, as evidenced by concentrations equivalent to 1 % of C_{max} measured just prior to the second dose.

Clinical Considerations

Gemtuzumab ozogamicin (Mylotarg®) was approved in May 2000 under the FDA's accelerated approval program. A confirmatory, post approval clinical trial

was undertaken in 2004. The trial was designed to determine whether adding GO to standard chemotherapy demonstrated an improvement in clinical benefit (overall survival) to AML patients. The trial was halted early when no improvement in clinical benefit was observed and after a greater number of deaths occurred in the group of patients who received Mylotarg® compared with those receiving chemotherapy alone. Due to the lack of survival advantage and serious safety concerns such as increased post-marketing rates of sinusoidal obstructive syndrome (SOS), the FDA withdrew GO from the market in June 2010; GO is not commercially available to new patients. Patients who are currently receiving GO may complete their therapy following consultation with their prescribing physician. Any future use of GO in the United States will require submission of an investigational new drug application to the FDA. Gemtuzumab ozogamicin was previously indicated for the treatment of CD33-positive AML in first relapse for patients greater than or equal to 60 years of age who are not candidates for other chemotherapy.

■ Rituximab, Yttrium-90 (^{90}Y) Ibritumomab Tiuxetan, Iodine-131 (^{131}I) Tositumomab

Pharmacology and Pharmacokinetics

Rituximab, the first MAB approved for the treatment of cancer, was approved for use in 1997. It is a chimeric murine/human MAB directed against the CD20 antigen found on nearly all B lymphocytes. Rituximab is approved in the United States for the following indications: treatment of relapsed or refractory, B-cell CD20-positive, low-grade or follicular NHL; first-line treatment of follicular or diffuse large B-cell (DLBCL) CD20-positive NHL in combination with chemotherapy; treatment of low-grade, CD20-positive B-cell NHL in patients achieving a response or stable disease to first-line chemotherapy; treatment of moderate to severe rheumatoid arthritis in combination with methotrexate; and treatment of Wegener's granulomatosis and microscopic polyangiitis in combination with glucocorticoids. Rituximab is widely utilized in an off-label fashion for numerous clinical conditions, and the final three indications represent the many current and future non-oncologic uses of this antibody. However, as this chapter focuses on oncologic indications, the non-oncology uses of rituximab will not be further discussed and the reader is referred to Chaps. 19 and 20 for the non-oncology use of rituximab (Fig. 17.2).

All normal B cells and greater than 90 % of malignant B cells contain the CD20 antigen (Maloney et al. 1994). CD20 is the human B-lymphocyte-restricted differentiation antigen, Bp35, and is a hydrophobic transmembrane protein. CD20 is involved with cell cycle initiation, regulation, and differentiation by activation of B cells from the G0 (resting) phase to the G1 (gap 1) phase, and CD20 has also been shown to operate as a calcium ion channel. Rituximab is thought to mediate death of CD20-positive tumor cells via activation of the complement cascade through at least three distinct mechanisms. Specifically, antibody-dependent cell-mediated cytotoxicity, direct effects via CD20 ligation, and complement-mediated apoptosis are all believed to play a role (Maloney et al. 1997). The depletion of B cells, via the CD20 antigen, can be extensive and prolonged.

The pharmacokinetics of rituximab were assessed in non-Hodgkin's lymphoma patients at a dosage of 375 mg/m^2 intravenously given weekly for 4 weeks (Maloney et al. 1994). The mean serum half-life increased throughout the study (76.3 h after the first week to 205.8 h after the fourth week). This increase is thought to occur secondary to depletion of the CD20 antigen. Without an antigen to bind to, rituximab's clearance will be reduced. After 4 weeks of treatment, rituximab may be detectable in a patient's serum for up to 6 months. After 8 weeks of weekly rituximab infusions using the same dose, the mean maximum concentration was found to increase from 243 μg/mL after the first infusion to 550 μg/mL after the final infusion.

In one study of 166 patients, B cells were depleted within the first three doses of rituximab and the depletion was maintained throughout 6–9 months in the majority of patients. B-cell levels should return to normal levels by 12 months after the last dose of rituximab.

When B cells become activated, they mature into plasma cells, the terminally differentiated B cell, and actively secrete immune globulins. With the use of rituximab, statistically significant reductions in IgG, IgM, and IgA have been observed. However, in the majority of cases, the levels remain normal.

Indications and Clinical Efficacy

Rituximab has been studied as a single agent in low-, intermediate-, and high-grade lymphomas. A review of low-grade lymphoma studies using single agent rituximab shows the ranges of overall response rate (OR), which is the complete response rate (CR) plus the partial response rate, and CR to be 27–73 % and 0–23 %, respectively. A review of intermediate- and high-grade lymphomas using single agent rituximab shows the ranges of OR and CR to be 14–73 % and 0–44 %, respectively.

Perhaps, the most studied chemotherapy used in combination with rituximab is the CHOP regimen which consists of cyclophosphamide, doxorubicin, vincristine, and prednisone. A phase III trial evaluated the addition of rituximab to CHOP versus CHOP alone in elderly patients with DLBCL (Coiffier et al. 2002). The combination provided statistically significant

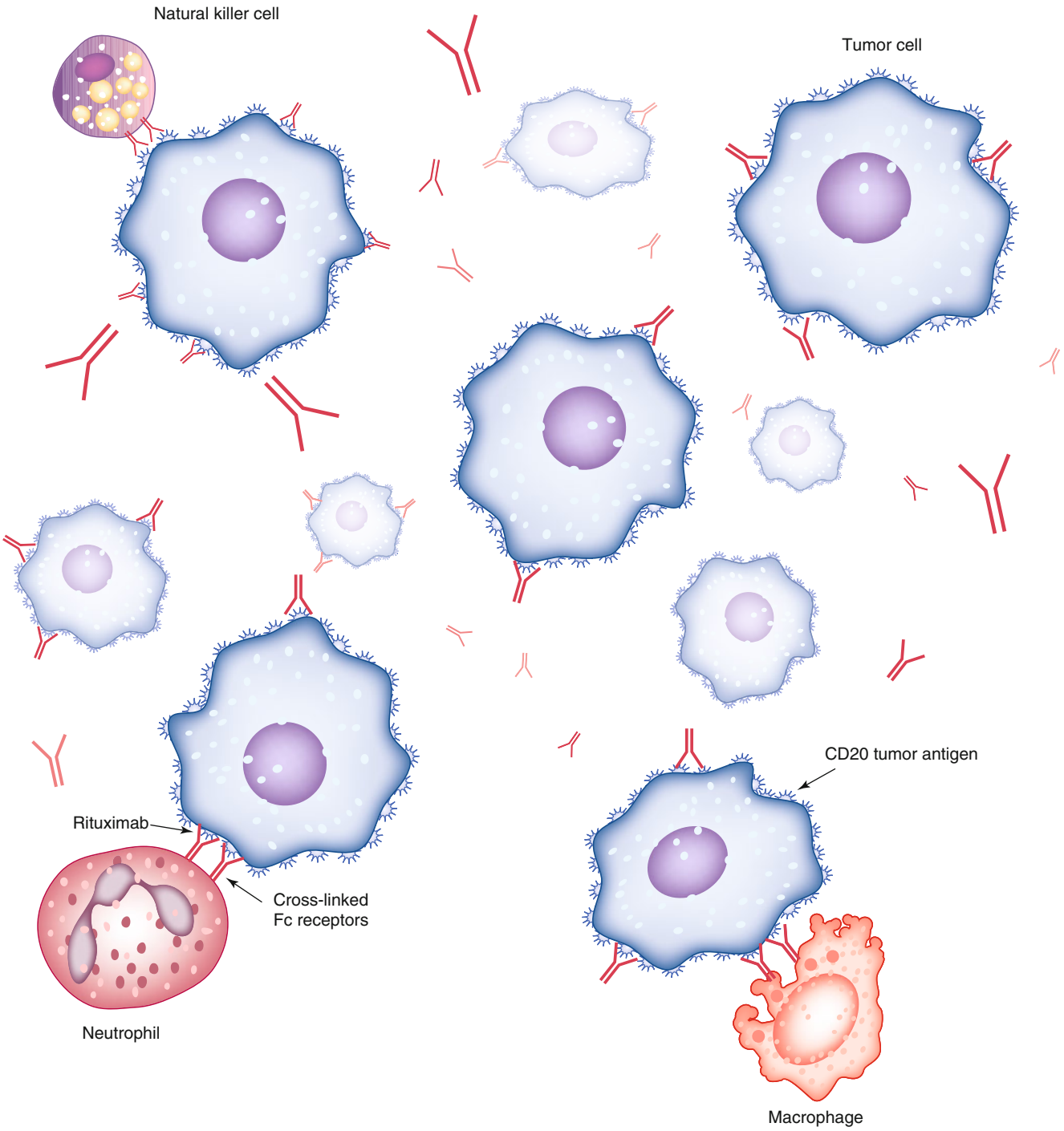

Figure 17.2 ■ Rituximab mechanism of action (*Source*: Point Therapeutics).

increases in clinical endpoints including CR, event-free survival, and overall survival, without increasing treatment-related toxicity. Rituximab in combination with chemotherapy regimens (mostly CHOP or CHOP-like regimens) achieves OR and CR in the range of 29–100 % and 11–85 % of patients, respectively (Coiffier 2002; McLaughlin et al. 1998; Plosker and Figgitt 2003).

Rituximab is increasingly used in the maintenance setting after achieving remission, particularly in low-grade lymphomas. The use of maintenance rituximab for 2 years significantly improves progression-free survival in patients with both previously untreated and relapsed follicular lymphoma who have responded to induction treatment. The safety of rituximab maintenance is consistent with the known safety profile of

rituximab, and long-term follow-up in maintenance trials will determine the effect on overall survival. At this time, the optimal schedule and duration of maintenance therapy remain to be determined (Hochster et al. 2009; Huang et al. 2012).

Rituximab is also used in conjunction with a MAB designed with a conjugated radionuclide. This radioimmunotherapy allows radiation to be delivered directly to the tumor site in an attempt to limit the radiation exposure and adverse effects to healthy tissues. Yttrium-90 (^{90}Y) ibritumomab tiuxetan was the first radioimmunoconjugated MAB approved by the FDA for treatment of relapsed or refractory follicular, low-grade, or transformed NHL. Rituximab is used in the ^{90}Y ibritumomab tiuxetan therapeutic regimen to clear the peripheral blood of CD20 found on normal B cells. This facilitates binding of the ^{90}Y ibritumomab tiuxetan to the CD20 antigen located on the tumor cells. Another radioimmunoconjugated MAB, iodine-131 (^{131}I) tositumomab, is a similar therapeutic regimen; however, tositumomab is used to clear the peripheral blood of CD20 instead of rituximab.

To date, there have been no head-to-head comparisons of these two radioimmunotherapies. However, ^{90}Y-ibritumomab tiuxetan was compared to rituximab in a phase III, randomized controlled trial for rituximab-naïve patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL (Witzig et al. 2002a, b). ^{90}Y-ibritumomab tiuxetan produced a statistically significant increase in CR (30 % vs 16 %) and OR (80 % vs 56 %, $p = 0.002$). However, there were no differences in time to progression.

Safety

Because rituximab is a chimeric MAB and contains mouse protein, infusion-related reactions can be significant. Infusion-related reactions, such as fever, chills, and myalgias, along with hypersensitivity reactions, such as bronchospasm, pulmonary infiltrates, hypotension, and angioedema, have occurred during rituximab infusions. Patients are more likely to experience these reactions when receiving their first infusion of rituximab, when tumor burden is most likely at its highest. The incidence decreases with subsequent infusions. Should an infusion reaction occur, the rituximab infusion should be discontinued immediately. If the infusion reaction was not severe and symptoms have resolved, the infusion may be restarted at half the previous rate at which the reaction occurred. All infusions should be preceded by premedication with an antihistamine and acetaminophen. For patients experiencing previous infusion-related reactions, additional premedication with corticosteroids may be required for subsequent dosing. Typical rituximab infusion times range from 3 to 6 h based upon dosage and tolerability, although many clinicians are choosing to administer it via a shorter, fixed rate if no previous hypersensitivity reactions have previously occurred (Salar et al. 2006; Sehn et al. 2007).

Rituximab's package labeling contains four black box warnings: fatal infusion reactions, tumor lysis syndrome (TLS), severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML). The majority (80 %) of fatal infusion reactions occur in relation to the first infusion. Reported infusion-related sequelae preceding death often include bronchospasm, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or anaphylactoid events. Those at higher risk for developing TLS are patients with NHL who have a high amount of circulating malignant cells or large tumor burden and those who have received concomitant cisplatin due to further risk of development of acute renal failure or death. Severe mucocutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have occurred within 1–13 weeks after receiving rituximab. Patients who experience a severe mucocutaneous reaction should be permanently discontinued from rituximab. PML is a rare and usually fatal condition that results from a JC virus infection and is characterized by progressive damage or inflammation of the white matter in the brain. If any patient presents with new-onset neurologic manifestations while receiving rituximab, a full workup for possible PML should ensue (Plosker and Figgitt 2003; Wood 2001).

Radioimmunotherapy

Due to the limited scope of this chapter, the two conjugated MABs, yttrium-90 (^{90}Y) ibritumomab tiuxetan and iodine-131 (^{131}I) tositumomab, have only briefly been mentioned in the context of the clinical efficacy section involving rituximab therapy. These agents have a limited therapeutic scope as their primary use is in radioimmunotherapy for treating indolent NHL. Yttrium-90 (^{90}Y) ibritumomab tiuxetan is comprised of a murine IgG_1 MAB ibritumomab that is linked to the radioisotope yttrium-90 by stable chelation via the linker, tiuxetan (Hagenbeek and Lewington 2005). Yttrium-90 is a beta-emitter of high energy with a long half-life (64 h). The drug is given as a single treatment consisting two components given approximately 1 week apart (i.e., rituximab administration followed by ^{90}Y-ibritumomab tiuxetan). Rituximab acts to reduce the number of healthy B cells so that ^{90}Y-ibritumomab tiuxetan will not destroy noncancerous cells. When ^{90}Y-ibritumomab tiuxetan is administered, it attaches to the CD20 proteins on the cell surface of B cells and releases energy from the yttrium radioisotope, killing the B cell. Patients with normal platelet function (i.e., $>150 \times 10^9$/L) should receive 0.4 mCi/kg of body

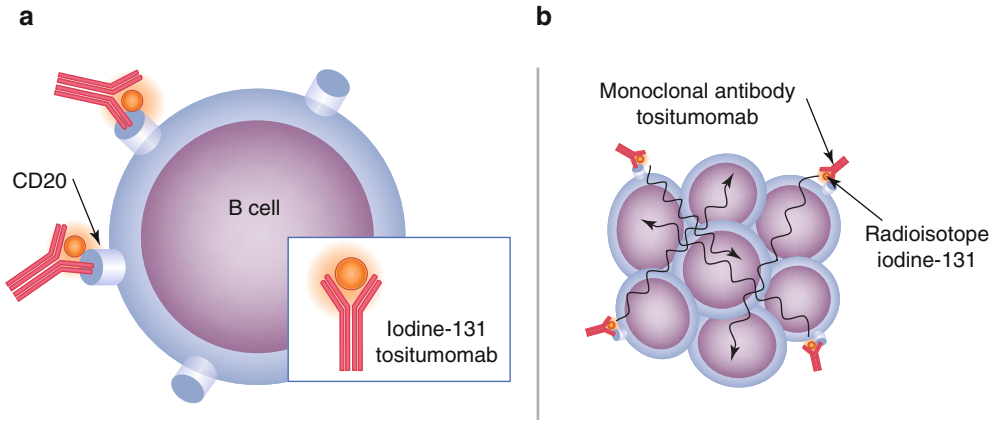

Figure 17.3 ■ Iodine-131 (^{131}I) tositumomab mechanism of Action. (**a**) Iodine-131 tositumomab binds to the CD20 antigen on normal and malignant B lymphocytes. (**b**) "Cross-fire" effect of iodine-131 in ^{131}I- tositumomab will cause damage to tumor cells as well as adjacent normal tissue (*Source*: GlaxoSmithKline).

weight up to a maximum of 32 mCi. Those with a platelet count between 100 and 149 × 10^9/L should receive a reduced dose of 0.3 mCi/kg, which has been shown to have equal efficacy to higher doses (Hagenbeek and Lewington 2005). The main safety concerns include myelosuppression with nadirs reached in 4–8 weeks after administration of therapy.

Iodine-131 tositumomab is another conjugated MAB that acts in a similar mechanism to ^{90}Y-ibritumomab tiuxetan although it emits both beta and gamma radiation. Specifically, it binds to the CD20 antigen found on B cells to kill them via two mechanisms: (1) activating an immune host response to B cells and (2) causing apoptosis in B cells to which it is bound as shown in Fig. 17.3.

■ Brentuximab Vedotin

Pharmacology and Pharmacokinetics

Brentuximab vedotin is an antibody-drug conjugate (ADC) that is directed against the CD30 antigen. CD30 is highly expressed on the surface of Hodgkin's lymphoma and anaplastic large cell lymphoma tumor cells (Francisco et al. 2003; Wahl et al. 2002; Younes et al. 2010). It is a member of the tumor necrosis superfamily. It was thought to be a promising target for MAB-based therapies since the normal expression of CD30 is limited for the most part to activated immune cells. Unfortunately, the CD30 MABs have shown little activity in clinical trials as compared to the anticancer activities demonstrated in preclinical studies (Wahl et al. 2002). In an effort to increase the potency of CD30-targeted MAB therapy, an ADC was created. It is made up of three parts which include a synthetic analog of dolastatin 10, monomethyl auristatin E (MMAE), that was conjugated to a chimeric IgG_1 antibody, cAC10, by a protease-cleavable linker that covalently attaches MMAE to cAC10, to create cAC10-vcMMAE (Francisco et al. 2003). The protease-cleavable linker is a highly stable dipeptide linker that is selectively cleaved by lysosomal enzymes after internalization. MMAE is a small molecule that is a microtubule-disrupting agent. It is suggested that the anticancer activity of brentuximab vedotin is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage by cathepsin, a lysosomal protease. The free MMAE binds to tubulin within the cell and disrupts the microtubule network which leads to G2/M cell cycle arrest and apoptotic death of the cells (Francisco et al. 2003).

Brentuximab is the first of the second-generation ADC to be approved. The principle behind ADC development is the concept that combining a cytotoxic drug to a MAB specific for an antigen that is more highly expressed on cancer cells could direct high doses of the cytotoxic drug specifically to the cancer cells and potentially avoid a large portion of the normal cells. Unfortunately, it has been difficult to obtain the desired outcome of this concept with various first-generation ADCs not demonstrating sufficient activity (Francisco et al. 2003). The second-generation ADCs are designed based on an improved understanding of several characteristics of ADCs. First, the chosen antigen should be one that would allow for substantial tumor selectivity. Second, the cytotoxic drug should be extremely potent since only a small amount of the ADC will come into contact with the tumor cell. Lastly, the linker technology should be of such that the ADC is stable while in circulation but effectively releases the active drug once it is internalized into the tumor cells (Francisco et al. 2003).

During preclinical experiments, in vitro data reflected that lysosomal enzymes effectively cleaved the dipeptide linker after brentuximab vedotin binding to CD30 and internalization into the cell (Francisco et al. 2003). The fully active drug MMAE was released into the cell cytosol and resulted in growth arrest in the G2/M phase, apoptosis, and cell death. The 50 % inhibitory concentration [IC_{50}] was<10 ng/mL and brentuximab was 300-fold less potent against antigen-negative cells.

The effect of brentuximab vedotin on the QTc interval was evaluated in an open-label, single-arm trial. Brentuximab vedotin was administered at 1.8 mg/kg to 46 evaluable patients with CD30-expressing hematologic malignancies.

The terminal half-life observed was approximately 4–6 days with steady state achieved in 21 days with every 3-week dosing. There was minimal to no accumulation of ADC with multiple doses on an every 3-week schedule. At the MTD of 1.8 mg/kg, the mean $AUC_{0–21days}$ was 76.65 day μg/mL with a maximum mean concentration of 32 μg/mL, obtained at a median time of 0.089 days (Younes et al. 2010). The maximum concentration for MMAE was achieved from approximately 2 to 3 days from administration with steady-state levels within 21 days with every 3-week dosing. Continued administration of brentuximab vedotin did result in decreased exposure to MMAE, with 50–80 % of the exposure of the first dose being observed with subsequent doses. At the dose of 1.8 mg/kg, the mean AUC_{0-21d} for MMAE was 0.036 day μg/mL with a maximum mean concentration of 0.005 μg/mL, obtained at 2.09 days (Younes et al. 2010) The mean steady-state volume was 6–10 L in humans. Approximately 68–82 % of MMAE is bound to human plasma proteins. Only a small portion of the MMAE that is released from brentuximab vedotin is metabolized. MMAE is metabolized by CYP3A4/5. It does appear that brentuximab vedotin also inhibits CYP3A4/5. The half-life of the ADC is 4–6 days, close to the half-life of MMAE of 3–4 days, and this is consistent with the steady-state kinetics occurring after approximately 21 days. The elimination of MMAE is limited by the rate it is released from ADC. In patients who received a dose of 1.8 mg/kg of brentuximab vedotin, about 1/4 of the total MMAE that was administered was recovered in feces and urine. Of the MMAE that was recovered, approximately 72 % was in the feces with the majority of MMAE unchanged. Data from population pharmacokinetic analysis does not demonstrate a significant impact of age, gender, or race on the pharmacokinetics of brentuximab vedotin.[8]

Indications and Clinical Efficacy

Brentuximab vedotin received FDA approval in August 2011 to treat Hodgkin's lymphoma and systemic anaplastic large cell lymphoma (ALCL). It is indicated in patients with Hodgkin's lymphoma after failure of autologous stem cell transplant (ASCT) or after the failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates. It is also indicated to treat patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen. The recommended dose of brentuximab vedotin is 1.8 mg/kg. It is administered as an intravenous infusion over 30 min every 3 weeks. For patients that weigh greater than 100 kg, the dose should be calculated using a weight of 100 kg (Ansell 2011). Patients continue on therapy up to a maximum of 16 cycles, disease progression, or intolerable toxicity. The dose of brentuximab vedotin should be reduced and/or delayed for peripheral neuropathy and neutropenia. Brentuximab vedotin received accelerated FDA approval for treating Hodgkin's lymphoma based on results from two phase II trials (Gopal et al. 2012; Younes et al. 2012). The first was an open-label, single-arm clinical trial which included 102 patients that had relapsed after receiving an autologous stem cell transplant. The overall response rate was approximately 73 %, and 32 % of the patients achieved a complete response. The median duration of response was 6.7 months. The second phase II open-label, single-arm trial was conducted in 58 patients with relapsed systemic anaplastic large cell lymphoma. All patients were relapsed after receiving prior therapy. Of the 58 patients, 72 % were anaplastic lymphoma kinase-negative. The overall response rate was 86 %. The complete response rate was 57 % and partial response rate was 29 %. The median duration of response was 12.6 months (Foyil et al. 2012).

Safety

The administration of brentuximab vedotin did not prolong the mean QTc interval >10 ms from baseline. It was stated that small increases in the mean QTc interval (<10 ms) could not be excluded due to the fact that the study did not include a placebo arm and a positive control arm. The safety of brentuximab vedotin was evaluated during two phase II trials (Furtado and Rule 2012; Skarbnik and Smith 2012; Younes et al. 2010). Brentuximab vedotin monotherapy was administered to 102 patients with relapsed or refractory Hodgkin's lymphoma and 58 patients with relapsed or refractory sACLC at a dose of 1.8 mg/kg every 3 weeks. In Hodgkin's lymphoma patients, the most common treatment-related adverse effects (AEs) of any grade that occurred in >15 % were peripheral sensory neuropathy (43 %), fatigue (40 %), nausea (35 %), neutropenia (19 %), diarrhea (18 %), and pyrexia (16 %). Grade 3 treatment-related AEs that occurred in >1 % of patients were neutropenia (14 %), peripheral sensory neuropathy (5 %), thrombocytopenia and hyperglycemia (3 %), and fatigue (2 %). The only grade 4 treatment-related AEs included neutropenia (4 %), and thrombocytopenia, abdominal pain, and pulmonary embolism that were reported at 1 % each. In the 58 patients with sACLC, the most

common treatment-related AEs reported were peripheral sensory neuropathy (41 %), nausea (40 %), fatigue (38 %), pyrexia (34 %), diarrhea (29 %), rash (24 %), constipation (22 %), and neutropenia (21 %). Grade 3 peripheral sensory neuropathy was reported in 17 % of patients and there were no reports of grade 4 or greater treatment-related AEs. Infusion reactions were reported in phase I and II trials. There were two cases of anaphylaxis in phase I trials and 12 % of patients reported grade 1 and 2 infusion-related reactions during phase II trials. The most common adverse reactions that were associated with infusions were chills (4 %); nausea, dyspnea, and pruritus (each at 3 %); and pyrexia and cough (both 2 %).[8] It is currently not recommended to premedicate all patients prior to brentuximab vedotin infusion. If a patient experiences an infusion-related reaction, they should receive premedication prior to subsequent doses, which can consist of acetaminophen, an antihistamine, and a corticosteroid (Furtado and Rule 2012; Gopal et al. 2012; Pro et al. 2012).

In January 2012, the FDA issued a new boxed warning for brentuximab vedotin based on postmarking reports of additional cases of progressive multifocal leukoencephalopathy (PML). Brentuximab vedotin should be held in patients with symptoms of PML and discontinued in patients diagnosed with PML (Wagner-Johnston et al. 2012). The use of brentuximab vedotin is contraindicated due to pulmonary toxicities. The rate of noninfectious pulmonary toxicity was higher with brentuximab given concurrently with bleomycin than the historical incidence of pulmonary toxicity reported with ABVD (Haddley 2012; Minich 2012; Oki and Younes 2012).

MMAE is metabolized in the liver via CYP3A4, and thus, brentuximab vedotin should not be administered with CYP3A4 inhibitors or inducers. Administration with strong inducers or inhibitors can alter the exposure of MMAE.

CLASSES OF MONOCLONAL ANTIBODIES: VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) INHIBITORS

Angiogenesis inhibitors have become standard therapies in multiple malignancies. As tumors enlarge, the centers become hypoxic and stimulate angiogenic growth factors, as shown in Fig. 17.4. Vascular endothelial growth factor (VEGF) is thought to be one of the most potent growth factors and has been shown to induce neovascularization for malignant cells in an autocrine fashion. High levels of VEGF have also been correlated with poor prognosis, disease recurrence, and metastases in a variety of neoplasms.

■ Bevacizumab

Pharmacology and Pharmacokinetics

Bevacizumab acts by binding and neutralizing the VEGF-A isoform. The depletion of VEGF downregulates the VEGF/VEGF receptor pathway, resulting in inhibition of new vessel formation and induction of a more normal tumor vasculature pattern leading to decreased vascular permeability (Ferrara 2004). The restoration of a more normal functioning vasculature within the tumor environment may improve delivery of concomitant chemotherapy and oxygen (Jain 2005). Bevacizumab is a humanized anti-VEGF monoclonal IgG_1 antibody. It was developed from a murine anti-human VEGF MAB and is 93 % human and 7 % murine. Similar to other IgG antibodies, a two-compartment model is used to describe the pharmacokinetics of bevacizumab. It has a relatively long elimination half-life and a limited volume of distribution (50–60 mL/kg). The initial half-life is 1.4 days with a prolonged terminal half-life of 20 days (Dirks and Meibohm 2010; Lu et al. 2008). The prolonged terminal half-life of bevacizumab permits for dosing schedules of every 2–3 weeks, allowing for bevacizumab to be dosed on the same schedule as most chemotherapy regimens.

Indications and Clinical Efficacy

Bevacizumab was first approved by the FDA in 2004 for the treatment of metastatic colorectal cancer and has since received approvals for the treatment of metastatic renal cell cancer, nonsquamous non-small cell lung cancer, and glioblastoma multiforme (Braghiroli et al. 2012). Bevacizumab was also granted accelerated approval for the treatment of breast cancer. This approval was subsequently withdrawn after trials failed to demonstrate an overall survival benefit.

In the treatment of metastatic colorectal cancer, bevacizumab is used primarily in addition to combination chemotherapy including the FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) and FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) regimens (Braghiroli et al. 2012). The addition of bevacizumab at a dosage of 5 mg/kg every 2 weeks to first-line chemotherapy in metastatic setting improves response rates, progression-free survival, and overall survival. Data also support the use of bevacizumab after failure of first-line chemotherapy in patients that have not yet received bevacizumab.

Lung cancer remains the number one cause of cancer-related death in the United States with over 150,000 attributable deaths annually. Non-small-cell lung cancer (NSCLC) accounts for 85 % of lung cancer cases and approximately 70 % of cases present with advanced disease. VEGF is among the proangiogenic factors contributing to blood vessel growth in NSCLC

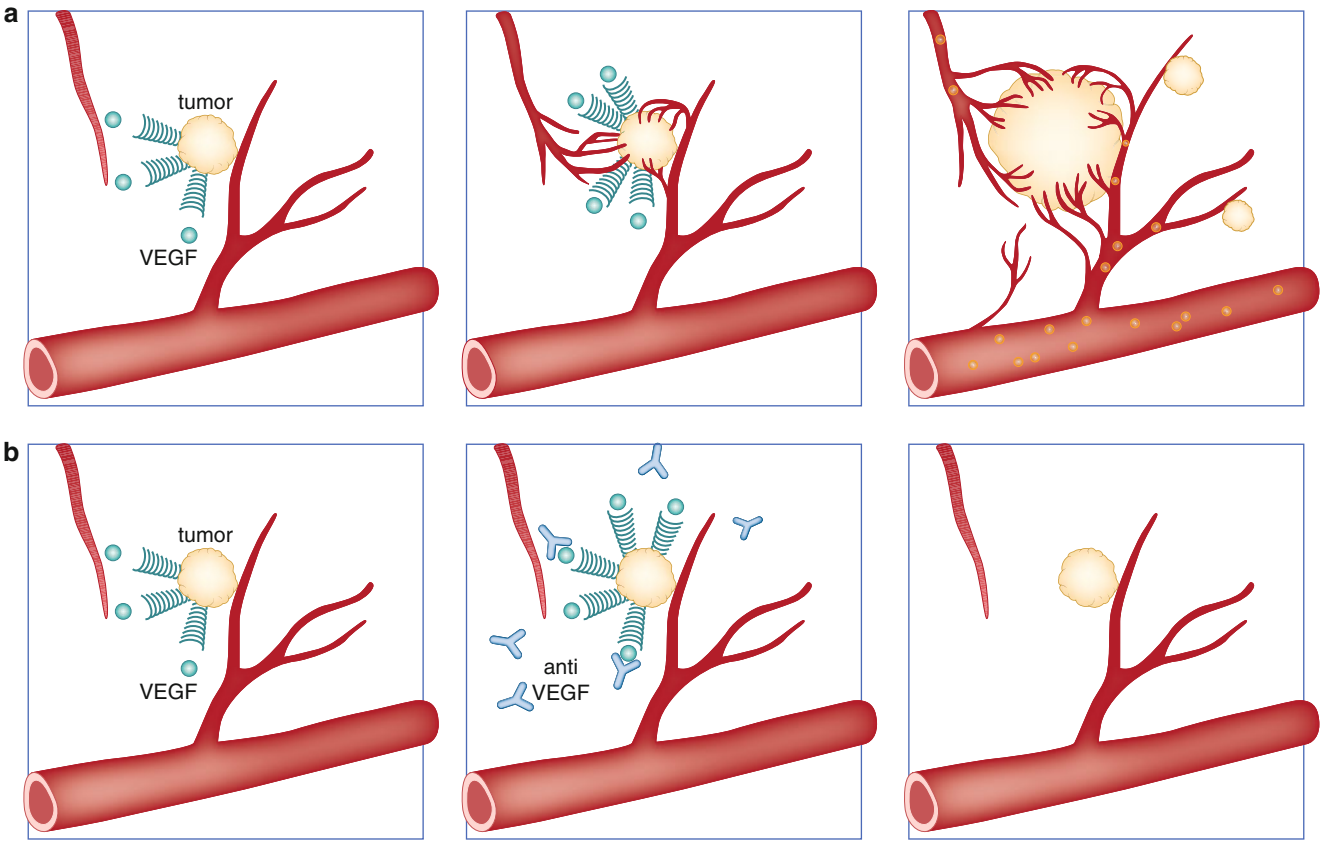

Figure 17.4 ■ Mechanism of action of vascular endothelial growth factor (VEGF) (**a**) and theorized mechanism of action of VEGF inhibitors (**b**) (*Source*: AJHP and GlaxoSmithKline).

(Planchard 2011). A phase II randomized clinical trial in patients with previously untreated advanced and recurrent NSCLC provided the first clinical evidence of benefit of antiangiogenic treatment in patients with NSCLC. Patients were randomized to one of three treatment arms: carboplatin plus paclitaxel, carboplatin plus paclitaxel with bevacizumab 7.5 mg/kg every 3 weeks, or carboplatin plus paclitaxel with bevacizumab 15 mg/kg (Johnson et al. 2004). Carboplatin and paclitaxel were continued for a maximum of four cycles, and bevacizumab was continued until disease progression or intolerable toxicity. The bevacizumab 15 mg/kg dose added to carboplatin and paclitaxel increased the response rate from 18.8 to 31.5 % and prolonged the median progression-free survival time by approximately 3 months. The patients with NSCLC of squamous cell histology tumors were noted to be at an excessive risk of bleeding complication from bevacizumab. The bleeding risk was partially attributed to the central location typical of squamous cell histology tumors. Patients with squamous cell histology were excluded from further clinical trials and it remains a contraindication for treatment with bevacizumab.

The phase III trial, E4599, was a landmark trial in the treatment of NSCLC (Sandler et al. 2006). It randomized patients with nonsquamous NSCLC to treatment with carboplatin and paclitaxel with or without bevacizumab at a dosage of 15 mg/kg every 3 weeks. Patients treated with bevacizumab had a significantly higher response rate (35 % vs 15 %), progression-free survival (6.2 months vs 4.5 months), and overall survival (12.3 months vs 10.3 months). A second phase III trial, AVAiL, evaluated bevacizumab (either 7.5 or 15 mg/kg every 3 weeks) in addition to a cisplatin plus gemcitabine chemotherapy regimen (Reck et al. 2012). The original primary endpoint was overall survival, but this was changed to progression-free survival after results from E4599 were released. The trial met its endpoint with a marginal improvement in progression-free survival of 0.6 months for the low-dose group and 0.4 months for the high-dose group. Overall survival was not significantly improved; however, the trial was underpowered for an adequate survival analysis. The results of this trial failed to confirm the findings of E4599. Further investigations continue to define the role of bevacizumab in the treatment of nonsquamous NSCLC.

Malignant gliomas account for approximately 70 % of malignant primary brain tumors, and glioblastoma multiforme (GBM) accounts for 60–70 % of malignant gliomas (Wen and Kesari 2008). In patients

with newly diagnosed GBM, the 5-year survival is consistently less than 5 %. GBMs are characteristically highly vasculature tumors suggesting a role for antiangiogenic therapies. Bevacizumab received accelerated approval for the treatment of GBM on the basis of randomized phase 2 trials. The BRAIN trial randomized 167 patients to bevacizumab 10 mg/kg every 2 weeks alone or the same dosage combined with irinotecan (Friedman et al. 2009). The overall response rate was 28.2 and 37.8 % in the bevacizumab and bevacizumab plus irinotecan arms, respectively. The median duration of progression-free survival was 4.2–5.6 months, respectively. Overall survival at 12 months was 38 % in both groups. A second phase II trial randomized patients to treatment with bevacizumab 10 mg/kg every 2 weeks in combination with either temozolomide or irinotecan. Approximately 40 % of patients in both treatment arms remained progression-free at 6 months. Safety data specific to this population of patients suggest that the rate of hemorrhage is significantly increased by the concomitant use of anticoagulants. Additionally, preoperative bevacizumab may significantly impair wound healing after second and third craniotomy even if surgery is more than 4 weeks after the last dose of bevacizumab (Clark et al. 2011). While definitive efficacy data endpoints of bevacizumab in GBM compared to other standard therapies remain to be seen, the current data available was sufficient to warrant FDA approval. The European Medicines Agency did not consider the current data sufficient owing to a lack of appropriate controls in trials to date and insufficient data correlating overall response rate to longer-term benefit such as improvement in overall survival (Specenier 2012).

Safety

Common adverse events attributable to bevacizumab include hypertension, proteinuria, and increased chemotherapy-induced neutropenia (Braghiroli et al. 2012; Specenier 2012). Although occurring less commonly, bevacizumab contributes to an increased risk for both thrombotic events and bleeds. Most commonly bleeding events that do occur are minor and limited to epistaxis. Because bevacizumab may delay wound healing, it is recommended to allow a minimum of 28 days from the last dosing of bevacizumab prior to any major surgical procedure.

CLASSES OF MONOCLONAL ANTIBODIES: ENDOTHELIAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS

The ErbB family of tyrosine kinase receptors consists of four members: EGFR (erbB-1, Her-1), Her-2/neu (erB-2/neu), erbB-3 (Her-3), and erbB-4 (Her-4). Signaling via EGFR and Her-2 in tumor cells is responsible for diverse cellular functions including proliferation, survival, adhesion, and DNA damage repair. Overexpression of EGFR family receptors has been noted in a wide variety of human cancers including breast, colon, gastric, rectal, lung, and squamous cell cancers of the head and neck. Four available monoclonal antibodies target members of this receptor family: trastuzumab and pertuzumab target the Her-2/neu receptor, while cetuximab and panitumumab are selective for EGFR.

■ Trastuzumab

Pharmacology and Pharmacokinetics

Trastuzumab is a recombinant DNA-derived humanized MAB (IgG_1 kappa) that selectively binds to the extracellular domain of the human Her-2 receptor with high affinity. This receptor-antibody interaction, through a series of other cellular actions, induces autophosphorylation of the tyrosine kinase internal domain resulting in decreased tumorigenic potential and possibly reversal of chemoresistance. Weekly administration of trastuzumab exhibits dose-dependent pharmacokinetics (Baselga et al. 1999; Leyland-Jones et al. 2003). When 10–500 mg doses (administered by short-duration intravenous infusions) were studied in women with metastatic breast cancer, the mean half-life increased and clearance decreased with increasing doses. The observed average half-life was 1.7 days for the 10 mg dose and 12 days for the 500 mg dose. However, in studies analyzing the commonly used regimen for trastuzumab of an initial loading dose of 4 mg/kg followed by a 2 mg/kg weekly maintenance dose, the mean half-life was 5.8 days. Studies also suggest that age and serum creatinine do not affect the disposition of trastuzumab. It is also important to note that when trastuzumab is administered in combination with paclitaxel, a 1.5-fold elevation in serum concentrations of trastuzumab is observed as compared to when trastuzumab is administered in combination with anthracycline and cyclophosphamide (Fig. 17.5).

Indications and Clinical Efficacy

Trastuzumab is indicated for the treatment of Her-2-positive breast cancer in the adjuvant and the metastatic setting and is also indicated for the treatment of Her-2-positive gastric cancer (Andersson et al. 2011; Bang et al. 2010; Guarneri et al. 2008; Seidman et al. 2008; Valero et al. 2011). In patients with breast cancer expressing Her-2, the addition of trastuzumab treatment for 1 year to adjuvant therapy improves overall survival. In the metastatic disease, adding trastuzumab to therapy will also increase disease response and improve survival. With the recent addition of pertuzumab, most metastatic breast cancer patients that would receive trastuzumab will now receive both therapies, as outlined in the following section on pertuzumab. The Her-2 receptor is also

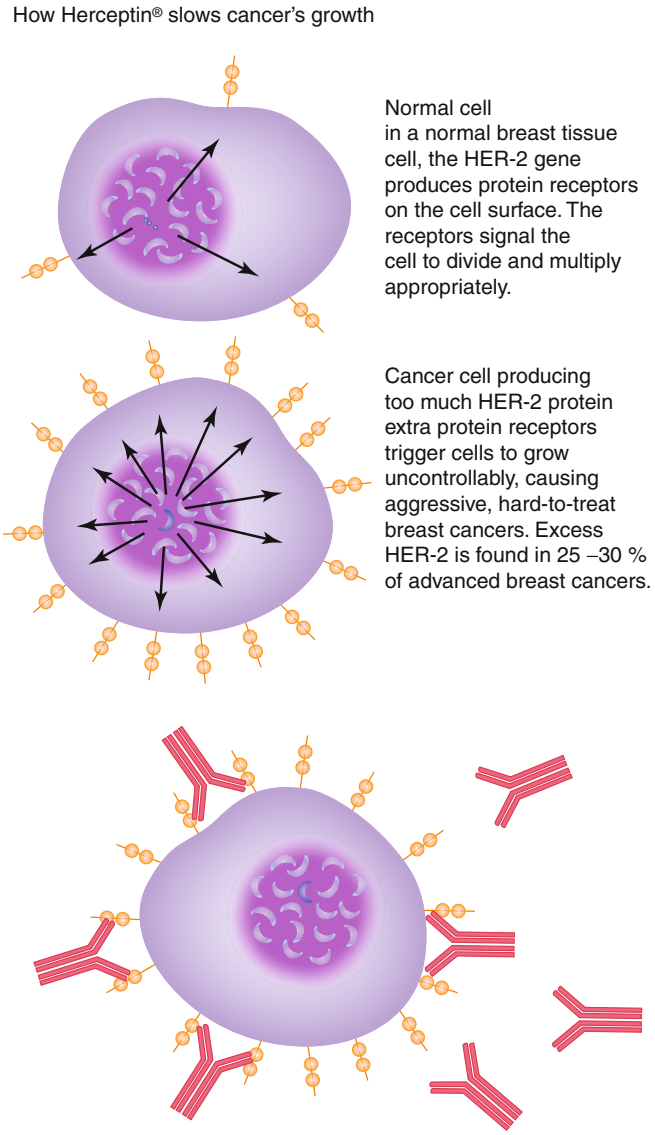

Figure 17.5 ■ Trastuzumab mechanism of action (*Source*: Dana-Farber Cancer Institute).

expressed on approximately 20 % of gastric cancers and the addition of trastuzumab to chemotherapy for gastric cancer has been demonstrated to improve overall survival by just under 3 months (Bang et al. 2010).

Safety

Trastuzumab has a black box warning for cardiomyopathy because of its potential to cause ventricular dysfunction and congestive heart failure. The severity and occurrence of cardiomyopathy was higher in patients who received anthracyclines and cyclophosphamide in combination with trastuzumab. Patients who require trastuzumab therapy must receive a full cardiac workup prior to the initiation of therapy and left ventricular function must be monitored during treatment. The most common adverse reaction is infusion reactions (usually mild to moderate), which rarely require discontinuation of therapy. Other adverse effects associated with trastuzumab are anemia and leukopenia, nausea/vomiting, diarrhea, and upper respiratory infections (Andersson et al. 2011; Guarneri et al. 2008; Seidman et al. 2008; Valero et al. 2011).

■ Pertuzumab

Pharmacology and Pharmacokinetics

Pertuzumab is a recombinant humanized MAB that selectively binds to the extracellular domain of the human HER-2 receptor. In contrast to trastuzumab, which binds to domain IV, pertuzumab binds to domain II and inhibits heterodimerization of HER2 with other HER family members. This inhibition prevents ligand activated HER activation and subsequent activation of intracellular pathways associated with proliferation and survival of cancer cells (Keating 2012). Pertuzumab has demonstrated activity against a number of cancer cell lines (breast, lung, ovarian, prostate, and colorectal). Tumor growth inhibition of >80 % was seen in breast cancer cell lines exposed to 5–25 μg/mL (Keating 2012) Improved anticancer activity was observed in patients treated with pertuzumab in combination with trastuzumab compared to either drug alone (Cortes et al. 2012).

A linear two-compartment model is used to describe the pharmacokinetics of pertuzumab (Ng et al. 2006). The mean volume of distribution at steady state is 4.23 L, with a clearance of 169 mL/day following a 420 mg dose. The mean elimination half-life is 19 days, allowing for every 3 week dosing. Simulated serum concentrations were similar with weight based and fixed dosing. A fixed dose regimen of an 840 mg loading dose followed by a maintenance dose of 420 mg every 3 weeks results in C_{min} serum concentration greater than the target of 20 μg/mL (Ng et al. 2006; Yamamoto et al. 2009). Steady-state is reached after the first maintenance dose (Keating 2012).

Indications and Clinical Efficacy

Pertuzumab is indicated for the treatment of HER-2 positive metastatic breast cancer in combination with trastuzumab and docetaxel for patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. In a randomized, controlled clinical trial of HER2 positive, recurrent or unresectable metastatic breast cancer patients, the addition of pertuzumab to trastuzumab and doxetaxel resulted in an increase of progression-free survival of 6.1 months and an overall survival benefit, HR = 0.66 (95 %, CI 0.52–0.89, $p = 0.0008$) (Baselga et al. 2012; Swain et al. 2013).

Patients discontinuing docetaxel due to adverse events could continue on treatment with the combination of pertuzumab and trastuzumab. Subset analysis revealed a benefit regardless of hormone receptor status, and regardless of prior adjuvant or neoadjuvant therapy.

Safety

Overall, pertuzumab appears well tolerated, adding minimally to the toxicity of docetaxel and trastuzumab (Baselga et al. 2012). Adverse events occurring in >5 % of patients in the pertuzumab arm compared to placebo include: diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin. Regular cardiac ejection fraction monitoring (every 3 months) is recommended, mostly due to the concomitant administration of trastuzumab, as pertuzumab did not add to the incidence of left ventricular systolic dysfunction. While infusion-related reactions have been reported, the routine use of premedication is not needed unless an infusion-related reaction has occurred and the patient is being re-challenged with pertuzumab treatment.

■ Cetuximab

Pharmacology and Pharmacokinetics

Cetuximab is a chimeric IgG_1 MAB composed of the Fv region of a murine anti-EGFR antibody with human IgG heavy and kappa light chain constant regions. It binds to the extracellular domain of EGFR with an affinity 5–10-fold greater than that of endogenous ligands (epidermal growth factor, amphiregulin, transforming growth factor). Cetuximab exerts its activity by blocking endogenous ligands, with a resultant inhibition of EGFR signaling. It also induces internalization of the receptor, which can further downregulate EGFR signaling. Further, binding of cetuximab to EGFR can target cytotoxic immune effector cells toward the EGFR-expressing tumor cells (Fig. 17.6).

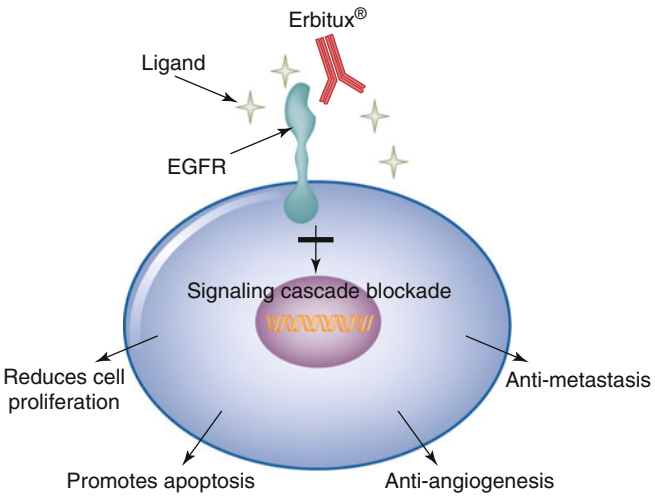

Figure 17.6 ■ Cetuximab mechanism of action. Cetuximab targets EGFR and binds to EGFR with higher affinity than its natural ligands. Binding results in the internalization of the antibody receptor complex without activation of the intrinsic tyrosine kinase. Consequently, signal transduction through this cell pathway is blocked, which inhibits tumor growth and leads to apoptosis. Other mechanisms of action include the inhibition of the production of angiogenic factors and synergistic activity with both radiotherapy and chemotherapy (*Source*: Merck KGaA).

Cetuximab pharmacokinetics were best described by a 2-compartment model with a saturable Michaelis-Menten-type elimination (Dirks et al. 2008). The AUC shows a greater than proportionate increase when the dose is increased from 20 to 400 mg/m^2. The drug clearance decreased from 0.08 to 0.02 L/h/m^2 with 20 and 200 mg/m^2 doses, with little change at higher doses. Steady-state levels were reached by week three of cetuximab infusions with a 114-h mean half-life when the recommended regimen of 400 mg/m^2 (loading dose) followed by weekly 250 mg/m^2 was administered (Delbaldo et al. 2005; Shirao et al. 2009). An extended dosing interval of 500 mg/m^2 every 2 weeks has been evaluated and demonstrated overall similar exposure and trough levels of cetuximab. The every 2-week dosing regimen may improve patient convenience, particularly when combined with every 2-week chemotherapy regimens. However, weekly dosing remains recommended in treatment guidelines because this dosing was used in the phase III trials.

Indications and Clinical Efficacy

Cetuximab is indicated in the treatment of metastatic colorectal cancer and squamous cell cancers of the head and neck. In the pivotal BOND trial, 329 patients with metastatic EGFR-expressing chemo-refractory CRC were randomized to receive cetuximab plus irinotecan or cetuximab alone (Cunningham et al. 2004). Both study arms received a 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly until either the patient had intolerable toxicities or disease progression occurred. The overall response rate was 22.9 % in patients receiving combination therapy (irinotecan plus cetuximab) and 10.8 % in the cetuximab monotherapy group. In addition, two prespecified subpopulations were analyzed: an irinotecan-oxaliplatin failure group (irinotecan refractory patients who had previously been treated with and failed an oxaliplatin-containing regimen) and the irinotecan refractory group. The irinotecan-oxaliplatin failure subpopulation had a 23.8 % response rate and a 2.9 month median time to disease progression for the cetuximab plus irinotecan study arm, and an 11.4 % response rate and 1.5 month time to progression for the cetuximab monotherapy study arm. There was no correlation between the level of the EGFR expression and response rate. However, KRAS mutation has since been discovered to be a predictive marker of benefit to treatment with EGFR-targeting MABs in patients with colorectal cancer.

KRAS is a G protein downstream of EGFR and is a critical component of EGFR signaling, propagating EGFR signaling events. Mutations in exon 2 or KRAS occurs in approximately 40 % of patients with colorectal cancer and can cause KRAS to be constitutively activated, which can render EGFR-targeting drugs ineffective (Karapetis et al. 2008). The CRYSTAL trial was a randomized, open-label, phase III trial in the first-line treatment setting that randomized metastatic colorectal cancer patients to treatment with infusional 5-FU, folinic acid, and irinotecan (FOLFIRI) alone or FOLFIRI plus cetuximab. In the patients testing positive for KRAS mutation, the progression-free survival was 7.4 and 7.7 months in the cetuximab and control arms, respectively. In the KRAS wild-type patients, the progression-free survival was 9.9 and 8.4 months in the cetuximab and control arms, respectively. Patients with colorectal cancer considered to be potential candidates for cetuximab should have tumor tissue tested for KRAS mutation status. If a mutation is present, the patient will not benefit from treatment with cetuximab.

Cetuximab is also used in the treatment of squamous cell cancers of the head and neck (SCCHN) in both patients with locoregionally advanced disease and in patients with recurrent and/or metastatic disease. The KRAS mutation rarely occurs in SCCHN and testing for it in this population is not recommended. In a phase III trial, cetuximab plus radiation therapy was compared to radiation alone in patients with squamous cell carcinoma of the oropharynx, hypopharynx, or larynx (Bonner et al. 2006; Specenier and Vermorken 2011). The standard dose of cetuximab, 400 mg/m^2 followed by 250 mg/m^2 weekly, was administered concomitantly with radiation therapy; control group patients received radiation therapy alone. Cetuximab prolonged the duration of locoregional disease control from 14.9 to 24.4 months. Median overall survival was improved from 29.3 to 49 months with cetuximab. The reported rates of radiation dermatitis were similar among the treatment groups in this trial. However, there have been subsequent reports of radiation dermatitis, including skin necrosis. Some authors have reported a 10-fold increase in the rates of radiation dermatitis with cetuximab and radiation compared to radiation alone (Koutcher et al. 2009; Studer et al. 2011). The standard chemotherapy and radiation treatment is a combination of cisplatin and radiation; a comparison of cetuximab and radiation to a cisplatin-treated control group is needed to determine which option is preferable.

Safety

Common adverse events associated with cetuximab include acneiform rash, diarrhea, hypomagnesemia, hypocalcemia, and infusion reactions (Specenier and Vermorken 2011). Acneiform rash develops in approximately 70–80 % of patients and is most prevalent on the trunk and face. Several treatment algorithms have been proposed and generally consist of treatments used for acne (Pinto et al. 2011). Mild rashes are treated with topical antibiotics (e.g., clindamycin gel or lotion). Treatment may be escalated to a course of treatment with oral antibiotics, primarily tetracyclines, if needed. For severe rashes, oral antibiotics in combination with a pulse of corticosteroids may be needed and treatment with cetuximab may need to be delayed until the rash resolves to a lower grade. Avoiding skin irritants, sun exposure, perfumes, and harsh cleansers may help to prevent and lessen the rash. Infusion reactions can be severe and occur in approximately 2–5 % of patients. Premedication with an antihistamine is required, and European product specifications also recommend the use of a corticosteroid premedication.

■ Panitumumab

Pharmacology and Pharmacokinetics

Panitumumab is a fully human, IgG_2 kappa MAB to the extracellular domain of EGFR. Although panitumumab shares the same target as cetuximab, the two monoclonal entities have two main differences. First, panitumumab is fully humanized, reducing the risk of immunogenicity. Second, in vitro studies have shown that panitumumab has a stronger affinity and specificity for EGFR compared to cetuximab (Cohenuram and Saif 2007).

In terms of pharmacodynamics, one preclinical study demonstrated that the tumor growth inhibition of panitumumab was related to a threshold EGFR level, where xenografts that contained at least 17,000 receptors per cell were treatable with panitumumab while those with less than 11,000 were not treatable (Yang et al. 2001). Similar to other EGFR inhibitors in clinical trials, increasing dose corresponded to an increasing frequency of an acneiform rash. In a phase I trial, patients that received 1, 1.5, 2, and 2.5 mg/kg weekly of panitumumab had 68, 95, 87, and 100 % incidence of rash with its apex at 3–5 weeks after starting therapy (Rowinsky et al. 2004). A post hoc analysis revealed that rash intensity trended toward a relationship with progression-free survival in patients.

Indications and Clinical Efficacy

Panitumumab is approved by the FDA for the treatment of EGFR-expressing, metastatic CRC with disease progression on or following fluoropyridine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. A randomized phase III trial compared supportive care alone or treatment with panitumumab (6 mg/kg intravenously) every 2 weeks in 463 patients with previously treated metastatic colorectal cancer;

prior treatment with cetuximab was not allowed. The mean progression-free survival was 96 days for the panitumumab group and 60 days for the other group (Saif and Cohenuram 2006). Eight percent of patients in the treatment arm exhibited a partial response and no observable response was observed in the control arm. There was no difference in overall survival between the two groups, although this may have been confounded by a significant proportion of patients from the BSC group that later crossed over to receive panitumumab.

The Panitumumab Advanced Colorectal Cancer Evaluation Study (PACCE) evaluated first-line FOLFOX with bevacizumab and FOLFIRI with bevacizumab with or without panitumumab. The trial was discontinued after an interim analysis indicated that the addition of panitumumab shortened progression-free survival and increased toxicity (Saif and Cohenuram 2006), suggesting that the addition of EGFR inhibition to anti-vascular-targeted therapy was detrimental.

Safety

Panitumumab has a black box warning for severe dermatologic toxicities and infusion reactions. Severe skin toxicities (grade 3 or higher) were reported in 12 % of patients to include acneiform dermatosis, pruritus, erythema, rash, and skin exfoliation. Severe infusion reactions (occurring in 1 % of patients) were also observed and include anaphylactic reactions, bronchospasms, fever, chills, and hypotension. However, the infusion reactions are less frequent than with cetuximab and no premedication is required (Cohenuram and Saif 2007; Saif and Cohenuram 2006). Pulmonary fibrosis has also occurred with panitumumab therapy. The more common adverse reactions include abdominal pain, hypomagnesemia, acneiform eruption (occurring in greater than 70 % of patients) and other skin rashes, paronychia, fatigue, nausea, vomiting, and diarrhea (Cohenuram and Saif 2007; Saif and Cohenuram 2006).

CLASSES OF MONOCLONAL ANTIBODIES: ANTIHUMAN CYTOTOXIC T-LYMPHOCYTE ANTIGEN 4 (CTLA-4)

The adaptive immune response to both pathogens and tumors is complex and multifactorial. Both CD4 helper and CD8 cytotoxic T cells contribute to adaptive immunity. Full T-cell activation requires multiple cosignals including major histocompatibility complex and costimulatory molecules (B7.1 and/or B7.2) (Lipson and Drake 2011). Human cytotoxic T-lymphocyte antigen 4 (CTLA-4) (CD152) plays a critical role in T-cell activation (Thompson and Allison 1997). CTLA-4 knockout mice expire of lymphoproliferative disorders within 3–4 weeks of birth (Waterhouse et al. 1995). CTLA-4 blockade leads to increased T-cell activation and blockade of CTLA-4 with a monoclonal antibody, ipilimumab, which became the first strategy to provide improvements in overall survival in patients with metastatic melanoma.

■ Ipilimumab

Pharmacology and Pharmacokinetics

Ipilimumab is a monoclonal antibody of the IgG_1 isotype that binds to human and cynomolgus CTLA-4 (Hanaizi et al. 2012). In preclinical animal models and toxicology studies, the major adverse reactions were immune mediated and included colitis, dermatitis, and infusion reactions. The pharmacokinetics of ipilimumab evaluated 498 patients with advanced melanoma. Doses ranged from 0.3 to 10 mg/kg administered once every 3 weeks for 4 doses. In this dose range, Cmax, Cmin, and AUC were dose proportional. Steady state was reached at the third dose. While clearance increases with increasing body weight and increasing lactate dehydrogenase (LDH), dose adjustments beyond the mg/kg dosing are not recommended (Hanaizi et al. 2012). The pivotal trials that provided the bulk of the clinical safety and efficacy data used a dosage of 3 mg/kg every 3 weeks for four doses, while other trials have used doses of 10 mg/kg; current clinical usage of ipilimumab is with the 3 mg/kg dosing (Hanaizi et al. 2012).

Indications and Clinical Efficacy

The first phase III trial to demonstrate an overall survival benefit in advanced melanoma was a 3-arm randomized controlled trial evaluating an experimental cancer vaccine, gp100, ipilimumab, or the combination of gp100 and ipilimumab (Hodi et al. 2010). Median overall survival was approximately 10 months in the patients receiving ipilimumab, which was a significant improvement compared to the 6.4 months in patients receiving gp100 monotherapy. A second phase III trial randomized patients to dacarbazine (850 mg/m^2) or dacarbazine plus ipilimumab. This trial used a dose of ipilimumab of 10 mg/kg (Robert et al. 2011). Patients receiving ipilimumab had an improvement in overall survival of approximately 2.1 months. No data regarding use in ocular melanoma are available yet. The addition of ipilimumab to the available standard of care treatments expands options available to patients and is the only therapy with a proven survival benefit without requiring selection based on B-Raf mutation.

Safety

The most frequently observed adverse events include diarrhea, rash, pruritus, and fatigue. Immune-mediated adverse events primarily involve the gastrointestinal tract (colitis) and the skin (rash and pruritus) (Hodi

et al. 2010). Less frequently, the liver, endocrine glands, and nervous system may also be involved. For mild and moderate symptoms, gastrointestinal and skin toxicities are generally managed symptomatically (Hanaizi et al. 2012). More severe symptoms may require a course of corticosteroids. This should be avoided if possible because of the potential to lessen the efficacy of the therapy. Hypopituitarism was reported in 4 % of patients and adrenal insufficiency, and hypothyroidism were each reported in 2 % of patients.

CLASSES OF MONOCLONAL ANTIBODIES: RECEPTOR ACTIVATOR OF NUCLEAR FACTOR KAPPA BETA LIGAND INHIBITOR

■ Denosumab

In breast and prostate cancer, nearly two-thirds to three-fourths of advanced disease will metastasize to the bone and approximately one-third of lung cancer patients will develop metastatic bone disease (Coleman 2004a, b). Bone metastases cause considerable skeletal morbidity and can reduce the patients' quality of life and decrease survival. Skeletal-related events (SREs) is a term that is used to describe a collection of adverse events associated with bone metastases and include pathologic fractures, the need for surgery or radiation to the bones and spinal cord and nerve root compression, and hypercalcemia of malignancy. Approximately half or more of patients with metastatic bone disease from breast, prostate, and lung cancer will experience an SRE within 2 years (Coleman 2004a, b).

For the last decade, bisphosphonate therapy with either pamidronate or zoledronic acid has been the cornerstone of treatment of bone metastases. Zoledronic acid is the only bisphosphonate to be evaluated for the prevention of skeletal complications in patients with bone metastases secondary to solid tumors other than breast or prostate cancer. It has been considered the standard of care for patients with breast cancer and the only bisphosphonate to show efficacy in patients with prostate cancer. Because of this, bisphosphonate therapy is the standard against which all novel treatments for bone metastases are compared. Because of poor bioavailability, bisphosphonate treatments for bone metastases are only available intravenously.

The receptor activator of nuclear factor κB ligand (RANKL) is produced by osteoblasts (and possibly osteoclasts as well) and binds to and activates RANK on osteoclasts. Once activated, RANK promotes osteoclast formation, function, and survival, which in turn promotes bone resorption. Denosumab binds to RANKL and prevents activation of RANK by RANKL thereby reducing bone resorption. In addition, the inhibition of bone resorption by osteoclasts reduces the production of growth factors that could enhance tumor growth as well as the release of osteoblast-inducing growth factors by the tumor (Romas 2009).

Denosumab is a fully humanized immunoglobulin G_2 (IgG_2) MAB that binds with high affinity and specificity to RANKL. The FDA approval of denosumab expanded the options available for the treatment of metastatic bone disease in patients with solid tumors.

Pharmacology and Pharmacokinetics

At doses below 60 mg, denosumab displays nonlinear pharmacokinetics but approximately dose-proportional increases in exposure at higher doses. Denosumab can be detected in the serum within an hour after subcutaneous administration. After a single dose, it can still be detected in the serum for up to 9 months. After multiple subcutaneous injections of denosumab at the approved dose of 120 mg every 4 weeks in patients with cancer and metastatic bone disease, up to 2.8-fold accumulation in serum denosumab concentrations was observed. Steady state was reached by 6 months and the mean serum trough concentration was 20.5 ± 13.5 μg/mL with a mean elimination half-life of 28 days (Gibiansky et al. 2012). In a population pharmacokinetic analysis of data from 14 clinical trials that included 1,076 individuals, the absolute bioavailability was 61 % following a subcutaneous injection and a mean absorption half-life of 2.7 days. Central volume of distribution was reported to be 2.61 L and the linear clearance was 3.3 mL/h. The clearance and volume of distribution were proportional to body weight. The steady-state exposures following repeat subcutaneous administration to 45 and 120 kg subjects were 48 % higher and 46 % lower, respectively, than exposure of the typical 66 kg individual. The linear fraction of the elimination of denosumab is thought to be mediated via the reticuloendothelial system.

Indications and Clinical Efficacy

Three phase III trials were conducted to review the efficacy of denosumab on SREs in patients with bone metastases (Henry et al. 2011; Stopeck et al. 2010). The three studies evaluated patients with breast cancer, prostate cancer, other solid tumors, and multiple myeloma. The same randomized, active-controlled, double-blind, double-dummy study design was utilized for all three trials. Patients were randomized in a 1:1 fashion to receive denosumab 120 mg subcutaneously plus intravenous placebo or intravenous zoledronic acid 4 mg plus subcutaneous placebo (with the dose adjusted for creatinine clearance) every 4 weeks. In the breast cancer and prostate cancer study, denosumab was noninferior with a trend to superior for the primary endpoint of time to first SRE as compared to zoledronic acid. In the third study, denosumab was

noninferior to zoledronic acid for time to first SRE. There was no difference in overall survival or disease progression within the two groups; however, in the subset of patients with multiple myeloma, it appeared to have a decrease in overall survival in the denosumab group. Therefore, denosumab is not indicated for the prevention of SREs in patients with multiple myeloma.

Safety

In the phase III clinical trials comparing denosumab to zoledronic acid in patients with bone metastases, there was a similar overall incidence of adverse events, including severe and serious adverse events (Henry et al. 2011; Stopeck et al. 2010). Over 96 % of patients in both arms reported an adverse event. However, patients were receiving concomitant medications, such as chemotherapy, and many of the adverse events reflected toxicities associated with the other medications. Adverse events of interest attributed to denosumab included infections, hypocalcemia, renal toxicity, acute-phase reaction, and osteonecrosis of the jaw (ONJ). When compared to zoledronic acid, denosumab was similar in infectious adverse events, with 43.4 % in the denosumab group as compared to 42.9 % in zoledronic acid. More patients receiving denosumab developed hypocalcemia (9.6 % vs 5.0 %) and there were similar rates of ONJ (1.8 % vs 1.3 %). On the other hand, more patients who received zoledronic acid experienced acute-phase reactions (20.2 % vs 8.7 %) as well as renal toxicities (11.8 % vs 9.6 %).

There are no contraindications to the use of denosumab, but data do not currently support its use in patients with multiple myeloma. Calcium levels, if low, should be corrected prior to the initiation of denosumab and monitored throughout therapy. Patients should be informed of the symptoms of ONJ which can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. An oral examination should be preformed and all appropriate preventive dentistry should take place prior to initiation of denosumab. Once a patient is on denosumab, it is recommended that they have periodical oral examinations (Henry et al. 2011; Stopeck et al. 2010).

CONCLUSION

MABs have become a cornerstone in the clinical management of a variety of solid and hematologic cancers. With a variety of different antibodies or antibody-based molecules in different stage of preclinical and clinical development, this role of MABs in cancer therapy will likely be further expanded over the next decade and will provide additional new benefits for patients suffering from cancer.

SELF-ASSESSMENT QUESTIONS

■ Questions

1. From the name "tositumomab and 131I tositumomab," what can one infer about the type of drug and origin?
2. The epidermal growth factor receptor inhibitors have a unique side effect profile which may also demonstrate a pharmacodynamic effect. Describe the profile and what development of this side effect may mean in terms of treatment effectiveness.
3. Describe the theory of angiogenesis and how vascular endothelial growth factor inhibitors may counteract this important mechanism of cancer development.
4. Bevacizumab is an angiogenesis inhibitor. List what is known about bevacizumab in terms of thrombotic and bleeding concerns. Are there any guidelines on duration of time between bevacizumab use after major surgery? What are they?
5. Describe the clinical literature that supported the FDA approval of panitumumab? What indication does it currently have?
6. Keeping rituximab's mechanism of action in mind, which of the following disease states would rituximab likely not show any benefit and why?
   (a) Autoimmune hemolytic anemia
   (b) Cutaneous T-cell lymphoma
   (c) Immune thrombocytopenic purpura
   (d) Rheumatoid arthritis
7. Which of the epidermal growth factor inhibitors require that patients test positive for the KRAS wild-type?
8. Trastuzumab and pertuzumab require a positive test for the expression of which receptor?
9. List the three black box warnings associated with rituximab use.

■ Answers

1. From the name "tositumomab and 131I tositumomab," one can infer several characteristics of this drug. First, it is a monoclonal antibody of murine origin, as designated by its suffix of "omab." Second, the drug is conjugated or radiolabeled since the drug name contains a second word containing one of the periodic elements.
2. The epidermal growth factor receptors (EGFR) inhibitors all share a common side effect profile that is dermatologic in origin. Generally, patients will present with an acneiform rash that cannot be successfully treated with over-the-counter acne agents. This rash is due to the fact that EGFR is overexpressed in many cancers as well as normal skin and hair follicles. Therefore, in some cases, the development of a rash may be associated with clinical efficacy of the drug.

3. For tumors to grow larger than 2 mm^3, they must begin to grow their own blood supply, both to provide oxygen and carry away wastes, a process known as angiogenesis. Several growth factors are necessary to stimulate angiogenesis; one of the most potent is vascular endothelial growth factor (VEGF). Bevacizumab is a VEGF inhibitor that prevents VEGF from binding to receptors, which subsequently prevents angiogenesis and tumor growth. Many think that VEGF inhibitors will be very successful in early stage disease where they can prevent large tumor growth, although bevacizumab is currently used more in a metastatic and late stage setting.
4. Evidence suggests that at least 28 days must elapse between a major surgery and subsequent bevacizumab administration. This is because antiangiogenesis inhibitors are associated with vascular dysfunction by their mechanism of action. There have been wound healing concerns, excessive bleeding, and even clotting concerns with the use of bevacizumab in clinical trials. Concomitant use of warfarin was shown to be safe in one recent clinical trial.
5. Panitumumab is currently indicated for "the treatment of patients with EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens" (i.e., third- or fourth-line use). This approval was based on a phase III trial ($n = 463$) that randomized patients to receive panitumumab monotherapy or best supportive care. The mean progression-free survival was 96 days for the panitumumab group and 60 days for the BSC alone group. Eight percent of patients in the treatment arm exhibited a partial response and no observable response was detected in the control arm.
6. Cutaneous T-cell lymphoma. This is because rituximab is a chimeric monoclonal antibody that binds to the antigen CD20 (cluster of differentiation 20), which is found on B lymphocytes (B cells).
7. In the treatment of colorectal cancer, both panitumumab and cetuximab are rendered ineffective by the activating KRAS mutation. Therefore, tumor tissue should be tested for KRAS and only those patients with a wild-type KRAS are likely to benefit from EGFR inhibitor MAB therapy.
8. Use of trastuzumab and pertuzumab requires a positive test for the HER-2/neu protein (i.e., a positive result either on fluorescence in situ hybridization (FISH) or immunohistochemistry (IHC) 2+) as clinical efficacy in the pivotal approval trials was related to overexpression of this protein.
9. Fatal infusion reactions, tumor lysis syndrome (TLS), and severe mucocutaneous reactions.

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