Monoclonal Antibodies and Side-Effect Management

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Monoclonal antibodies are increasingly becoming a standard part of clinical cancer treatment. Eight monoclonal antibodies are approved by the Food and Drug Administration for the treatment of cancer in the United States. Oncology nurses are expected to be familiar with these agents, their indications, and their adverse effects, to provide appropriate care and symptom management to patients receiving these agents, and to adequately educate patients and families about these treatments and their specific and overlapping side effects. Monoclonal antibody mechanisms of action and indications, infusion guidelines, and symptom management are outlined in this article.

Monoclonal antibodies (MoAbs) represent an important part of the targeted therapy approach to treat cancer. MoAbs specifically target tumor cells and may potentially cause fewer adverse effects on normal cells. The side effects of MoAbs depend on the specific target (or antigen) of the antibody, the type of cell where the antigen is expressed, and sometimes the tumor burden.

The history of monoclonal antibodies as an immunotherapeutic option dates back to the 19th century, when the toxin from diphtheria bacteria was isolated. The therapeutic potential of monoclonal antibodies began to be more fully realized in the 1970s, when Kholer and Milstein reported their Nobel Prize winning work on developing a process to generate specific monoclonal antibodies on a large scale in the laboratory.[1] Improvements in technology have yielded monoclonal antibodies specific to cell surface targets and soluble growth factors.[1-3] In the last decade, the Food and Drug Administration (FDA) has approved several MoAbs for the treatment of cancer, a total of eight as of May 2006 (Table 1). This article reviews six of the approved anti-cancer monoclonal antibodies, their side-effect profiles, and symptom management strategies.
Antibodies recognize and bind to specific antigens. Depending on the particular class and subtype, an antibody can interact with other serum proteins, such as the complement system, or Fc-receptors on cells to activate normal immune functions that selectively eliminate the antigen or totally eliminate the target cell expressing that antigen.

Antibodies are large (180 kDa) Y-shaped molecules containing two antigen binding Fab sites (represented by the arms of the Y and known as the variable region) and an Fc segment (represented by the stem of the Y and known as the constant region) (Figure 1). The Fc segment interacts with and activates specialized serum proteins. Known as complement, these serum proteins assemble into large macromolecular structures that lyse the membrane of cells that bind to the antibody. In addition, the Fc portion of the antibody may bind to receptors on immune cells and engulf or attack the targeted cell, a phenomenon termed antibody dependent cellular cytotoxicity (ADCC).

The Fab sites selectively recognize and bind to specific cell targets. Once the Fab arms attach to the intended target, the stem (Fc) calls in the immune system. This antibody/antigen complex acts as a warning flag, attracting other immune cells to destroy the antibody/antigen complex,[2,4,5] the cell bound to the antibody, or the tumor.

Overview of Monoclonal Antibodies

MoAbs differ from more typical anticancer drugs. Much larger chemical structures than drugs such as doxorubicin, MoAbs have very different properties and pharmacology. For example, doxorubicin is metabolized and excreted in 72 hours, while it is still possible to measure blood levels of the
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monoclonal antibody rituximab (Rituxan) 6 months after the last dose. Antigens are cell surface proteins that function as targets for binding monoclonal antibodies. MoAbs have been used to target host tissues or proteins that support tumor growth, such as growth factors and growth factor receptors. Monoclonal antibodies may also inhibit the binding of growth factors to their respective receptors on the cell surface and shut off downstream signaling that stimulates tumor cell growth. MoAbs with this mechanism of action are bevacizumab (Avastin), cetuximab (Erbitux), and trastuzumab (Herceptin)[1,2,6] and will be described in more detail later. To overcome this deficiency, scientists engineered antibodies to incorporate human antibody elements, particularly in the Fc portion of the antibody. One type of engineered antibody, known as a chimeric antibody, is part mouse and part human. The variable (Fab) portion of the mouse antibody is joined to the constant (Fc) portion of the human antibody. The mouse portion recognizes the antigen and the human portion recruits the immune system. Another type of engineered antibody, the humanized antibody, is mostly human (95%-98%) with only a small portion of the variable region (Fab) containing nonhuman sequences. The monoclonal antibody preserves its ability to recognize and bind to the target antigen via the mouse portion, provides effective immune activation via the human portion, and limits the possible neutralizing response to the antibody.[2,4,5,8]

Conjugated vs Unconjugated
Therapeutic MoAbs come in two forms: unconjugated or conjugated. Unconjugated monoclonal antibodies are unmodified and do not have cytotoxic agents or radioisotopes attached to them. Their antitumor activity solely results from the actions of the MoAb on their targets. The biologic activities generated by unconjugated monoclonal antibodies are outlined in Table 2. Examples of unconjugated MoAbs include rituximab, trastuzumab (Herceptin), cetuximab (Erbitux), and bevacizumab (Avastin).

Conjugated monoclonal antibodies have been modified by being physically attached to antitumor agents such as radioisotopes, chemotherapy drugs, toxins, or other biological agents. After targeting specific antigens, conjugated MoAbs attack tumors by releasing the attached antitumor agents into the cells or by or attracting and concentrating high levels of local radioactive emissions to the site. Examples of conjugated MoAbs include the radiolabeled MoAbs yttrium-90 ibritumomab tiuxetan (Zevalin) and iodine-131 tositumomab (Bexxar).[1,2,5,9] These are the only two murine MoAbs approved for cancer treatment and their administration requires highly specialized training with radioisotopes, which is beyond the scope of this article. Another example of a conjugated MoAb is gemtuzumab ozogamicin (Mylotarg), with the anti-CD33 MoAb conjugated to the cytotoxic antibiotic q1-calecheamicin.

Bevacizumab
Bevacizumab is a recombinant humanized IgG1 MoAb. It works by binding to human vascular endothelial growth factor (VEGF) and preventing the interaction of VEGF with VEGF receptors (VEGFR) on the surface of endothelial cells. Once VEGF binds, activated cellular tyrosine kinases transmit signals intracellularly from the receptor to the cell nucleus, causing endothelial cell proliferation and angiogenesis. By binding soluble VEGF, bevacizumab inhibits VEGF from binding to
its receptor and from signaling tumor neovascularization and ultimately tumor cell growth.[10-15]

Bevacizumab was approved by the FDA as first-line therapy in combination with intravenous fluorouracil (5-FU)-based chemotherapy for patients with metastatic colorectal carcinoma. Bevacizumab also is being studied in a number of clinical trials for the treatment of metastatic renal cell carcinoma, and pancreatic, breast, and non-small-cell lung cancer (NSCLC).[16-18] Side effects related to bevacizumab include hypertension, proteinuria, hemorrhage, thrombosis and poor wound healing. Table 3 includes infusion instructions for bevacizumab and Table 4 outlines side effects and their management.
Cetuximab
Cetuximab is a chimeric IgG1 monoclonal antibody targeting the extracellular domain of the epidermal growth factor receptor (EGFR/HER1).[1] Cetuximab binds EGFR on normal cells and on cancerous cells. Binding of EGFR by cetuximab interferes with stimulatory signal transduction to the cell nucleus, thus inhibiting cell proliferation, angiogenesis, cell adhesion, and motility, while enhancing apoptosis.[1,19]
Cetuximab was approved by the FDA for the treatment of EGFR-expressing metastatic colon cancer as a single agent or in combination with irinotecan (Camptosar)-based chemotherapy.[20] More recently, cetuximab was approved for first-line treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) in combination with radiation therapy, or as a single agent for recurrent or metastatic SCCHN after failure of prior platinum-based chemotherapy.[21] Cetuximab is also being evaluated in clinical trials for the treatment of NSCLC, pancreatic, cervical, rectal, recurrent epithelial ovarian, and primary peritoneal carcinoma.[22,23]
A major side effect of cetuximab is skin rash described as acneform, follicular, or maculopapular, that usually appears on the face, back, and chest. The rash typically occurs within the first 3 weeks of initiation of therapy.[19,24] Pérez-Soler and colleagues provided a detailed review of the potential causes as well as management recommendations for rash associated with EGFR/HER1 inhibitor therapy.[25] Table 3 includes infusion instructions for cetuximab and Table 5 outlines side effects and recommendations for symptom management.
Alemtuzumab

Alemtuzumab (Campath) is a humanized IgG1 rat monoclonal antibody targeting the CD52 antigen. CD52 is expressed at high levels on most lymphocytes, natural killer cells, monocytes, and macrophages. Alemtuzumab depletes normal and malignant lymphocytes by causing cell lysis through a variety of mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytolysis (CDC), and apoptosis.[26-29] Alemtuzumab was approved by the FDA in 2001 for the treatment of B-cell chronic lymphocytic leukemia (CLL) refractory to alkylating agents and fludarabine (Fludara). Alemtuzumab has also shown activity in T-cell prolymphocytic leukemia (T-PLL) and cutaneous T-cell lymphoma (CTCL).[30] Under investigation is alemtuzumab's potential as a treatment for a variety of autoimmune disorders, including autoimmune hemolytic anemia, multiple sclerosis, and rheumatoid arthritis.[31-33]

Alemtuzumab is administered intravenously with daily dose escalations, starting at 3 mg on day 1, and moving to 10 mg on day 3, then 30 mg on day 5, followed by 30 mg three times/week for 12 to 18 weeks. Infusion instructions for alemtuzumab are included in Table 3. The serum half-life of alemtuzumab is 15 to 21 days.[34]

Patients are premedicated with diphenhydramine and acetaminophen 30 minutes prior to treatment to prevent infusion-related side effects. The most common side effects are rigors, fever, nausea, vomiting, rash, urticaria, dyspnea, and hypotension.[34] The symptoms are thought to result from cytokine release by natural killer (NK) cells, and the intensity and frequency decreases after the first infusion. Systemic adverse effects may be minimized with subcutaneous administration of alemtuzumab.[35]

Sixty-five percent of patients who receive alemtuzumab experience lymphopenia and opportunistic infection, often manifested as reactivation of cytomegalovirus (CMV) or herpes virus infections.[36] One study reported that 51 of 93 of patients (55%) treated with alemtuzumab experienced one or more infections, 25 of them developing life-threatening infections including septicemia.[37] With prophylaxis, serious opportunistic infections are uncommon, but CMV reactivation is still frequent.[37] The overall incidence of CMV reactivation with alemtuzumab therapy is 15% to 25%.[38] Patients treated with alemtuzumab should receive antimicrobial prophylaxis until the peripheral blood CD4+ cell count returns to > 200/mm$^3$. Updated guidelines for managing reactivation of CMV are listed in Table 6.
While cardiotoxicity has been reported occasionally in patients treated with alemtuzumab,[36,39,40], the mechanism of cardiotoxicity is unknown. It is hypothesized that it may be related to cytokine release.[36] Previous administration of anthracyclines may be a risk factor for alemtuzumab-induced cardiac toxicity.[34]

Rituximab
The first monoclonal antibody approved for the treatment of cancer, rituximab is a chimeric IgG1 monoclonal antibody targeting the CD20 antigen expressed on the surface of B cells. Rituximab's mechanism of action includes the induction of apoptosis, inhibition of cell growth, activation of complement-mediated cell lysis, and induction of ADCC.[41] Rituximab was approved by the FDA in 1997 for the treatment of low-grade or follicular lymphoma, relapsed, or refractory CD20-positive non-Hodgkin's lymphoma. Recently, the FDA granted approval for use of rituximab as first-line treatment for patients with diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone) or other anthracycline-based chemotherapy. Rituximab has also been approved to treat rheumatoid arthritis.

Rituximab is dosed intravenously at 375 mg/m² weekly for 4 weeks.[42] Infusion instructions for rituximab are included in Table 3. The half-life of rituximab was found to be 76.3 hours with the first infusion, but increases to 205.8 hours after the fourth infusion. Up to 6 months after administration, rituximab can still be detected in the blood.[43]

Side effects observed with rituximab include acute infusional reactions, ranging from fever, chills, nausea, vomiting, rash, pruritis, and angioedema, to bronchospasm, dyspnea, and hypotension.[1,44] Cytokine release syndrome has been noted and is associated with increased levels of serum interleukin-6 and tumor necrosis factor alpha. Tumor lysis syndrome also has been reported. Patients are premedicated with acetaminophen and diphenhydramine prior to infusion. Infusional reactions are treated by stopping the MoAb infusion, readministration of histamine blockers, and restarting the infusion at half the rate at which the reaction occurred. Patients with a high tumor burden, pulmonary insufficiency, or pulmonary infiltrates should be closely monitored during treatment.

Trastuzumab
Trastuzumab is a recombinant humanized IgG1 monoclonal antibody directed against the extracellular domain of the HER2/neu protein.[1] HER2/neu is a member of the epidermal growth factor receptor family and is overexpressed in 20% to 30% of breast cancers. Overexpression is associated with a poorer prognosis.

Trastuzumab was approved in 1998 as a single agent for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who have received one or more chemotherapy regimens for metastatic disease. Trastuzumab was also approved for use in combination with paclitaxel for patients with metastatic breast cancer whose tumors overexpress HER2 and who have not received chemotherapy for metastatic disease. Recent trials provided overwhelming evidence that trastuzumab used in combination with chemotherapy in the adjuvant setting reduced tumor recurrences by half among women with early-stage HER2-positive breast cancer.[45]
Binding of trastuzumab is thought to disrupt the dimerization and signaling of the HER2/neu receptor.[46] This results in G1 phase cell cycle arrest and decreased cell proliferation, induces antiangiogenic factors, suppresses VEGF secretion, and facilitates ADCC.[47,48] The level of HER2/neu overexpression is essential to selecting appropriate patients for this therapy. Patients with low levels of HER2 expression do not benefit from trastuzumab.[49] Patients treated with trastuzumab receive a loading dose of 4 mg/kg administered over 90 minutes, followed by weekly maintenance doses of 2 mg/kg over 30 minutes. Infusion instructions for trastuzumab are included in Table 3. The plasma half-life of trastuzumab is 5.8 days, with steady state kinetics reached between 16 and 32 weeks.

Common side effects include mild to moderate chills, fever, nausea, and respiratory symptoms with initial dose.[50-52] Abdominal pain, diarrhea, vomiting, headaches, and rash also occur and increase in frequency when trastuzumab is used in combination with chemotherapy. Cardiac toxicity is the most serious side effect associated with trastuzumab therapy. A meta-analysis of seven phase II and III trials revealed higher rates of cardiotoxicity (27%) when trastuzumab was combined with an anthracycline and cyclophosphamide.[53] As a single agent, the frequency of cardiotoxicity associated with trastuzumab is about 7%, but most of these patients had received previous anthracycline drugs.

**Gemtuzumab Ozogamicin**

Gemtuzumab ozogamicin is an antitumor, antibiotic, humanized IgG4 monoclonal antibody conjugated to $\gamma_1$-calicheamicin, a powerful antitumor agent that damages cellular DNA, and targeting the CD33 antigen expressed on acute myeloid leukemia (AML) cells. The CD33 antigen is found on the surface of leukemic blasts and immature normal cells of myelomonocytic lineage, but is lacking on normal hematopoietic stem cells. Once gemtuzumab is bound to CD33, it is internalized and the $\gamma_1$-calicheamicin is released, then binds to cellular DNA, and nicks the strands causing cell death.[1,54]

AML is the most common acute leukemia among adults and its incidence increases with age.[1,54] More than 90% of patients with AML have blast cells expressing CD33.[1,54,55] Gemtuzumab ozogamicin was approved by the FDA for the treatment of patients with CD33-positive AML who are in first relapse, are 60 years or older, and are not candidates for other cytotoxic chemotherapy.[55] Several clinical trials are evaluating gemtuzumab ozogamicin as therapy for myelodysplastic syndromes and in combination with cytotoxic chemotherapy agents for the treatment of AML.[56] The recommended dose of gemtuzumab ozogamicin is 9 mg/m$^2$ infused over 2 hours. Infusion instructions are included in Table 3. Side effects include infusion-related reactions, including chills, fever, hypotension, and hypersensitivity reactions. Infusion-related symptoms generally occur with the first infusion or within 24 hours of infusion. In patients experiencing clinically significant hypotension or dyspnea, gemtuzumab ozogamicin infusion should be interrupted and the patients should be monitored until the symptoms are resolved.[54,55] Patients with high circulating blast counts are at greater risk for pulmonary events and acute tumor lysis syndrome and should be considered for leukoreduction with hydroxurea or leukapheresis to reduce the peripheral white count to below 30,000/µL prior to administering gemtuzumab ozogamicin.[55]

Severe hepatic veno-occlusive disease (VOD) has been reported, including death from liver failure and VOD. Patients should be monitored for hepatic symptoms which could include weight gain, right upper quadrant pain, hepatomegaly, ascites, and elevations in bilirubin and/or liver enzymes.[54,55] Hematological toxicities including granulocytopenia and thrombocytopenia are frequent and can be severe. Other side effects may include nausea and vomiting, tachycardia, stomatitis, and headaches.[1,54]

**Summary**

Monoclonal antibodies are increasingly becoming a standard in the care of some patients with cancer. Oncology nurses should be familiar with these agents as well as with their indications and side-effect profiles in order to provide appropriate care and symptom management to patients receiving these novel agents.

**References:**


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