FAST FACTS AND CONCEPTS #277
TARGETED CANCER THERAPIES - Part 2 of 2

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Background 'Targeted cancer therapy' is an umbrella term for a diverse group of newer antineoplastic agents. *Fast Fact* #276 focused on tyrosine kinase inhibitors (TKIs). This *Fast Fact* focuses on monoclonal antibodies (mAbs), the second major group of targeted cancer agents.

Monoclonal antibody development Antibodies are generated from a single clone of immune cells, and are directed against one specific epitope on the surface of cancer cells. MAbs can be derived from mouse, human, or hybrid elements; newer developments favor human-only in order to minimize anti-murine inflammatory response by the patient and to maximize target antigen specificity (1-4). MAb nomenclature reflects its derivation: -omab (entirely murine derived); -ximab (human-murine chimera); -zumab (up to 90% human); -mumab (entirely human). Since the first approval of rituximab as cancer therapy targeting CD 20 in 1997, the development of monoclonal antibodies targeting different antigens have been progressing fast. The recent FDA approvals of nivolumab and pembrolizumab highlight the fervor for mAbs targeting immune checkpoints to regulate endogenous antitumor activity.

Modes of action of monoclonal antibodies Unlike TKIs, the large size of mAbs necessitates they have activity on cell surfaces where they can induce immune responses against targeted cancer cells or interfere with proteins necessary for cell growth. Targeted activity may be enhanced by linking "naked" mAbs to other agents, including cytotoxic drugs or radioisotopes. They can be used as single agents, or combined with chemotherapy or hormonal therapy.

Side effects and complications of mAbs Common side effects of mAbs include allergic reactions, infusion reactions, flu-like symptoms, pneumonitis, gastrointestinal distress with nausea, vomiting and/or diarrhea, hypotension, skin rashes, and cytopenias. Premedicating patients with acetaminophen, antihistamines, steroids, and non-steroidal anti-inflammatory drugs prior to mAb administration is a standard part of preventative treatment (5). Important drug-specific side effects are outlined below (6,7).

Management of specific side-effects

Cardiovascular:

- Congestive heart failure (CHF): Monitoring cardiac function by close physical examination, laboratory assessment, EKGs and serial echocardiograms is indicated with some of the mAbs (e.g. trastuzumab) and in symptomatic patients. Standard treatment of CHF with ACE inhibitors, beta-blockers, diuretics and/or aldosterone receptor blockers is indicated. A left ventricular ejection fraction below 40% usually precludes starting or continuing many mAbs.
- Hypertension*:* As with TKIs, mild to moderate hypertension requires only observation. For moderate to severe hypertension, no specific drug guidelines exist and the hypertension is treated empirically. If hypertension cannot be managed, mAb treatment is discontinued.
- Thromboembolism: A complication of VEGF mAb therapy (e.g. bevacizumab), risk factors include age >65 and a history of thromboembolic events. Some clinicians empirically use aspirin to try to prevent thromboembolism (8).

Dermatologic: skin toxicities from EGFR monoclonal antibodies (e.g. panitumumab, cetuximab) are often more severe than from TKIs. However, evidence-based prevention or management guidelines do not exist. (9) Tetracyclines are often employed for management of acneiform rash.

Hypersensitivity reactions: The majority of these reactions are mild and occur within 30 minutes to two hours after the first or second exposure of the agent. *Rituximab*, *alemtuzumab*, *trastuzumab* and *cetuximab* are particularly associated with infusion reactions. Symptoms are felt to be secondary to cytokine release and may include fevers, rigors, flushing, chest discomfort, skin rashes, nausea or diarrhea. Immediate discontinuation of the infusion and administration of oxygen, intravenous normal saline to prevent/treat hypotension and intravenous antihistamines are indicated. Subcutaneous or intravenous epinephrine, inhaled beta-agonists to address potential bronchospasms and intravenous corticosteroids may be required in severe cases or anaphylaxis.

Table. Side effect profiles of 12 FDA-approved mAbs to treat malignancies (8,10-14)

Drug	Indications	Common side-effects	Serious side-effects	Target
Alemtuzumab (*Campath*)	B-cell chronic lymphocytic leukemia (CLL)	Myelosuppression, cytopenias, hypotension, fever, chills	Cardiac arrhythmias, cardiomyopathy, congestive heart failure, Grave's disease, CMV- and/or EBV infections	CD52 on T- and B-lymphocytes
Bevacizumab (*Avastin*)	Colorectal, non-small cell lung cancer (NSCLC), kidney, ovarian cancers; glioblastoma multiforme	Abdominal pain, nausea, vomiting, diarrhea, constipation, headaches, hypertension, proteinuria, asthenia, upper respiratory infections	Hypertension, thromboembolic events (arterial and venous), hemorrhages, bowel perforation, wound dehiscence	Vascular endothelial growth factor (VEGF)
Brentuximab vedotin (*Adcetris*)	Relapsed/ refractory Hodgkin's and anaplastic large cell lymphomas	Sensory neuropathy, cytopenias, diarrhea, nausea, vomiting, rash, cough, fatigue	Supraventricular cardiac arrhythmias, pneumonitis, pneumothorax, pulmonary embolism, PML	CD30. The microtubule disrupting component MMAE binds to tubulin.
Cetuximab (*Erbitux*)	Metastatic K-Ras negative colorectal cancer (CRC), squamous cell cancer of head/ neck	Acneiform rash, alopecia, pruritis; hypomagnesemia; diarrhea, nausea, constipation, insomnia; depression (especially in patients receiving irinotecan)	Sudden cardiac death, renal failure, interstitial lung disease, pulmonary embolism	Epidermal growth factor receptor (EGFR)
Ibritumomab Tiuxetan (*Zevalin*)	Refractory non-Hodgkin lymphomas (NHL)	Hypertension, cytopenias; rash, abdominal pain, diarrhea, nausea,	Severe cytopenica, with hemorrhage, Stevens-Johnson syndrome, toxic epidermal necrolysis, increased risk of myelodysplasia/ AML	CD20. Is linked to a radiation chelator (Tiuxetan - binds to Yttrium-90)
Ipilimumab (*Yervoy*)	Unresectable or metastatic malignant melanoma	Rash, pruritus, diarrhea, fatigue	Pericarditis, adrenal insufficiency, hypopituitarism, hypothyroidism, intestinal perforation, pneumonitis, Guillain-Barre syndrome	Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)

Nivolumab (*Opdivo*)	Unresectable or metastatic malignant melanoma, Metastatic NSCLC, Renal cell carcinoma (RCC)	Rash, pruritus, headache, Musculoskeletal pain,	Pneumonitis, colitis, hepatitis, hypophysitis, adrenal insufficiency	Programmed death receptor-1 (PD-1)
Ofatumumab (*Arzerra*)	Refractory CLL	Rash, diarrhea, nausea, anemia, pneumonia, fatigue, fever	Bowel obstruction, viral hepatitis, infectious diseases, PML	CD20
Panitumumab (*Vectibix*)	EGFR-expressing CRC	Acneiform rash, pruritis, exfoliative dermatitis, paronychia; hypomagnesemia, hypocalcemia; cough, dyspnea, peripheral edema, fatigue	Dermatologic toxicities, interstitial lung disease, pneumonitis, pulmonary fibrosis	EGFR
Pembrolizumab (*Keytruda*)	Unresectable or metastatic malignant melanoma, Metastatic NSCLC	Fatigue, decreased appetite, rash, pruritus, cough, arthralgia, diarrhea	Pneumonitis, colitis, hypophysitis, hypothyroidism, hyperthyroidism, hemolytic anemia, nephritis	PD-1
Pertuzumab (*Perjeta*)	Metastatic HER2-positive breast cancer in combination with trastuzumab and docetaxel	Alopecia, diarrhea, nausea, vomiting, inflammation of mucous membranes, rash, peripheral neuropathy, anemia, fatigue	Neutropenias with or without fever, hypersensitivity reactions, left ventricular cardiac dysfunction	Extracellular dimerization domain of the human epidermal growth factor receptor 2 (HER2) protein.
Rituximab (*Rituxan*)	B-cell NHL, CLL	Infusion reactions (fever, hypotension, shivering); abdominal pain, diarrhea, nausea, arthralgias, myalgias	Cardiac arrhythmias, cardiogenic shock, cytopenias, renal toxicities, angioedema, tumor lysis syndrome	CD20
Tositumomab (*Bexxar*)	CD20-positive NHL lymphoma	Abdominal pain, nausea, vomiting, Hypothyroidism, athenia, headache, cough, fever	Cytopenia, increased risk of myelodysplasia/ AML, pleural effusions, pneumonia, anaphylaxis	CD20. Is administered as “naked” mAb followed by mAb linked to the cytotoxic radioisotope I-131

Trastuzumab (*Herceptin, Herclon*)	HER2/neu overexpressing breast cancer, some gastric adenocarcinomas	Loss of appetite, diarrhea, nausea, vomiting, stomatitis, cough, dyspnea, edema	Cardiac dysfunction (especially with anthracyclines); respiratory failure, hepatotoxicity	Extracellular domain of the HER2 protein

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