PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #276
TARGETED CANCER THERAPIES - Part 1 of 2

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Background 'Targeted cancer therapy' is an umbrella term for a diverse group of newer antineoplastic agents developed to block the growth and progression of malignant cells by interfering with intracellular pathways responsible for tumor growth (1). Their use in treating cancer is expanding rapidly, including for patients with far-advanced disease who may not otherwise have been eligible for traditional cytotoxic chemotherapies (2). This *Fast Fact* reviews types of targeted cancer therapies and side effects seen with tyrosine kinase inhibitors (TKIs). *Part 2* addresses monoclonal antibody targeted agents.

Pharmacology While conventional chemotherapies generally interfere *non-selectively* with the proliferation of all rapidly dividing cells in the body, targeted agents are meant to block one or more molecules essential for the proliferation of cancer cells. They can be categorized into two main groups.

- *Small molecule drugs* are primarily TKIs. These are orally administered drugs with potential to inhibit various tyrosine kinases (TKs), intracellular enzymes that are mutated or over-expressed in malignant cells (3). TKIs competitively inhibit adenosine triphosphate at the catalytic binding site of the enzymes, compete with the substrate of TKs, or bind at alternative sites and induce a conformational change resulting in inhibition of the enzyme activity. Side-effect profiles of the TKIs depend on the roles the individual enzymes play in intracellular signaling and overall cell function. On-target toxicities are related to the primary pharmacological effects of the drugs and occur when TKIs inhibit molecules/ pathways that are required for normal function of cells at sites other than the cancer cells, while off-target toxicities are due to secondary pharmacological effects of the drugs and occur when molecules/ pathways are inhibited that are not intended to be targeted by the TKI (4). The Table summarizes many TKI's clinical use and toxicities.
- *Monoclonal antibodies* (mAbs) are larger than TKIs and unable to enter cells. They are designed to bind selectively to specific tumor-associated antigens on the surface of cancer cells. MAbs are administered intravenously and can be used either in an unconjugated form or conjugated via a linker to cytotoxic molecules to help enhance their tumor selectivity and their anti-cancer effect (5). MAbs are more specific than TKIs, but due to their complex development process, more expensive than TKIs.

Common side effects of TKIs All TKIs can cause cytopenias and gastrointestinal side effects such as nausea/vomiting (3). Some TKIs cause headaches, muscle cramps, periorbital edema, and induce/ worsen symptoms of depression. Since TKIs are teratogenic, female patients of reproductive age should take appropriate measures to prevent pregnancy and/or stop breast-feeding during therapy. Although patients may be evaluated for specific risks prior to therapy (e.g. premorbid cardiovascular disease) no guidelines exist for prophylaxis against TKI toxicities. Side effects should be managed with general symptom management principles (6). Two main classes of side effects are discussed below.

Cardiovascular toxicities:

- Mild to moderate hypertension requires only observation. For severe hypertension, there are no specific antihypertensive drugs which are recommended, except that nondihydropyridine calcium channel blockers (e.g. verapamil, diltiazem), which inhibit CYP3A4, should be avoided in conjunction with sunitinib and pazopanib (7).
- Left ventricular dysfunction manifestations range from asymptomatic EKG findings to severe heart failure. Predisposing factors include prior anthracycline therapy and TKI-induced hypertension (8).
- Pulmonary arterial hypertension (e.g. from dasatinib) is generally reversible with discontinuation (8).
- QTc interval prolongation occurs variably; whether this complication is class-wide is unknown. Although specific guidelines are lacking, caution is advised in patients with underlying cardiac disease and when other QTc prolonging drugs (such as many commonly used anti-emetics) are administered (8). Obtaining a baseline EKG is common, although empiric, practice.

Dermatologic toxicities:

- A variety of nonspecific skin toxicities may occur with TKIs, including dry skin, hair color changes, skin discoloration, acral erythema, subungual hemorrhages, an acneiform rash, and hand-food syndrome, beginning several weeks after therapy initiation.

- Prior to initiating therapy, patients are advised to use sunscreens, enhance skin moisturizing, and avoid tight fitting shoes (9).
- No specific management guidelines exist for the acneiform rash; expert opinion recommends topical antibiotics (e.g. clindamycin 1% +/- benzoyl peroxide) or oral antibiotics (e.g. tetracycline, minocycline) and continuation of TKI therapy (9).
- *Hand-foot syndrome* (HFS, or palmar-plantar erythrodysesthesia) often arises within the first 6 weeks of therapy, worsens with continued chemotherapy (10). HFS usually resolves within 2-4 weeks of drug therapy interruption, and usually recurs if TKI is introduced at the same dose. Expert opinion suggests National Cancer Institute Grade 1 HFS (erythema without pain) be treated with keratolytics and emollients; Grade 2 HFS (skin changes and/or pain) requires topical corticosteroids and topical or systemic analgesics (including opioids); Grade 3 (ulcerative dermatitis and/or pain impeding function) requires TKI interruption and dose reduction. Other supportive therapies in use - all empiric – include pyridoxine, COX-2 inhibitors, gabapentinoids, systemic corticosteroids, regional cooling, and transdermal nicotine (10).

Table. Side effect profiles of 20 FDA-approved TKIs to treat malignancies (7)

Drug	Indications	Common side-effects	Serious side-effects	Comments
Axitinib (*Inlyta*)	Renal cell cancer (RCC)	Hypertension, hand-foot syndrome, diarrhea, nausea, vomiting, transaminitis	Hemorrhages, arterial/ venous thrombosis, pulmonary embolism	
Bosutinib (*Bosulif*)	Philadelphia chromosome positive chronic myelogenous leukemia (CML)	Diarrhea, nausea, vomiting, abdominal pain, skin rash, thrombocytopenia	Prolonged QT interval, pericardial/pleural effusion, hepatotoxicity, acute renal failure	
Cabozantinib (*Cometriq*)	Metastatic medullary thyroid cancer	Electrolyte abnormalities (calcium, phosphorus), hypertension, cytopenias, transaminitis, hair color change, fatigue	Hand-foot syndrome, arterial and venous thromboembolism, cytopenias, gastrointestinal perforation and fistula formation	Discontinue drug before elective surgeries or dental procedures.
Crizotinib (*Xalkori*)	ALK-positive non-small cell lung cancer (NSCLC)	Vision disorder, diarrhea, nausea, vomiting, constipation, edema	Prolonged QT interval, transaminitis and hepatotoxicity, neutropenia, pulmonary embolism, pneumonitis	
Dabrafenib (*Tafinlar*)	Malignant melanoma with BRAF V600E mutation	Hyperglycemia, hypophosphatemia, headache, hyperkeratosis, alopecia, hand-foot syndrome, arthralgias, fever	New primary skin cancer (malignant melanoma, squamous cell cancer), pancreatitis, interstitial nephritis	Should be taken on an empty stomach.

Dasatinib (*Spycel*)	CML, Philadelphia chromosome positive acute lymphoblastic leukemia (ALL)	Body fluid retention, rash, headache, dyspnea, electrolyte abnormalities	Congestive heart failure, pericardial/pleural effusion, prolonged QT interval, hemorrhagic colitis	
Erlotinib (*Tarceva*)	NSCLC, pancreatic cancer (in combination with gemcitabine)	Diarrhea, edema, nausea, vomiting, loss of appetite, abdominal pain, rash, alopecia, cough, depression, fatigue, fever	Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, cardiac dysrhythmia, myocardial infarction, syncope, bowel obstruction, interstitial lung disease, corneal perforation/ulceration, abnormal eyelash growth	Cigarette smoking may require dose adjustment. Increased rash severity has been associated with better drug response and clinical outcome (4).
Gefitinib (*Iressa*)	NSCLC	Acneiform or pustulous rash, folliculitis; paronychial inflammation, diarrhea	Respiratory compromise (especially in patients with prior chemotherapy or radiation), interstitial lung disease, tumor hemorrhage	Co-administration of aspirin reduces the rash. Monitor INR frequently in patients who also take Warfarin.
Imatinib (*Gleevec*)	Gastrointestinal stromal tumors (GIST), certain types of leukemias (CML, Philadelphia chromosome positive ALL)	Rash, diarrhea, vomiting, arthralgia, edema, headache, weight gain	Left ventricular dysfunction, congestive heart failure, cardiac tamponade, cardiogenic shock, gastrointestinal perforation, sensorineural hearing loss, acute respiratory failure, increased intracranial pressure	Cardiac complications are usually seen in elderly with preexisting cardiovascular disease.
Lapatinib (*Tykerb*)	HER-2-positive breast cancer	Diarrhea, nausea, vomiting, hand-foot syndrome, rash, anemia, transaminitis, hyperbilirubinemia, fatigue	Prolonged QT interval, left ventricular dysfunction, hepatotoxicity, interstitial lung disease	Hepatotoxicity may necessitate drug discontinuation.
Nilotinib (*Tasigna*)	CML	Pruritus, night sweats, rash, diarrhea, nausea, vomiting, arthralgias, myalgias, headache, cough, fatigue, alopecia	Prolonged QT interval, cytopenias, gastrointestinal hemorrhage, intracranial hemorrhage	Must be taken on an empty stomach, as concomitant intake of food may increase the risk of QT prolongation.

Pazopanib (*Votrient*)	RCC, soft tissue sarcoma	Hypertension, changes of hair color, diarrhea, nausea, vomiting, loss of appetite, arthralgias, myalgias, headache, electrolyte abnormalities, dyspnea, fatigue	Hemorrhage, hepatotoxicity, congestive heart failure, myocardial infarction, hypothyroidism, reversible posterior leukoencephalopathy syndrome, pneumothorax	Cardiovascular and hepatic toxicities are usually seen within the first 18 weeks of treatment.
Ponatinib (*Iclusig*)	TKI-resistant CML, TKI-resistant Philadelphia chromosome positive ALL	Hypertension, abdominal pain, constipation, nausea, headache, fever	Arterial and venous thromboembolism, hepatotoxicity, body fluid retention, congestive heart failure, cardiac arrhythmias, myocardial infarction, cytopenias, pancreatitis	Co-administration of drugs that increase gastric pH may lead to decreased ponatinib bioavailability and exposure.
Regorafenib (*Stivarga*)	Colorectal cancer, GIST	Hypertension, electrolyte abnormalities, acral erythema, cytopenias, transaminitis, hyperbilirubinemia, difficulty speaking, proteinuria, fever	Hemorrhage, hepatotoxicity, hypertension, myocardial infarction, gastrointestinal fistula, gastrointestinal perforation	
Ruxolitinib (*Jakafi or Jakavi*)	Myelofibrosis	Contusion, dizziness, headache, anemia, thrombocytopenia	Cytopenias. Herpes zoster or serious infections may occur.	Dose adjustment may be required dependent on the platelet count.
Sorafenib (*Nexavar*)	RCC, hepatocellular cancer	Diarrhea, nausea, loss of appetite, abdominal pain, electrolyte abnormalities, fatigue, rash, hand-foot syndrome, alopecia	Hemorrhage, congestive heart failure, myocardial infarct, prolongation of QT interval, severe skin reactions	
Sunitinib (*Sutent*)	RCC, GIST, pancreatic neuroendocrine tumors	Diarrhea, nausea, vomiting, loss of appetite, altered taste sensation, yellow skin discoloration, rash, elevation of uric acid, hypothyroidism, cough, fatigue	Thrombocytopenia, tumor hemorrhage, prolongation of QT interval, left ventricular dysfunction, tissue necrosis, aseptic necrosis of jaw bone, hemoptysis, hepatotoxicity	Hypertension and proteinuria improve with dose reduction or discontinuation of the drug.
Trametinib (*Mekinist*)	Malignant melanoma with BRAF V600E or V600K mutation	Rash, diarrhea, transaminitis, anemia, lymphedema, hypoalbuminemia	Cardiomyopathy, hemorrhages, dermatologic toxicities, interstitial lung disease, pneumonitis, visual disturbances	

Vandetanib (*Caprelsa*)	Medullary thyroid cancer	Rash, acne, hypertension, hypocalcemia, transaminitis, headache, fatigue	Prolonged QT interval, ischemic stroke, interstitial lung disease, respiratory failure/arrest	Co-administration of anti-arrhythmic drugs should be avoided.
Vemurafenib (*Zelboraf*)	Malignant melanoma with BRAF V600E mutation	Nausea, arthralgias, alopecia, photosensitivity, pruritus, rash, skin papillomas	Squamous cell carcinoma, hand-foot syndrome, prolonged QT interval, ophthalmologic reactions (iritis, photophobia, retinal vein occlusion)	

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