Targeted therapy: What does the internist really need to know?

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This to acknowledge that Jonathan E. Dowell, MD has disclosed that he does have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Dowell will be discussing off-label uses in his presentation.

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Purpose/Educational Objectives: The purpose of this presentation is to familiarize the audience with the typical toxicities and drug interactions associated with the commonly used molecularly targeted agents in oncology. At the conclusion of this lecture, the listener should be able to:

1) Recognize the common and serious side effects of the VEGF inhibitors
2) Recognize the common and serious side effects of the EGFR inhibitors
3) Understand the cardiac risk of HER-2 directed therapy
4) Understand the cardiovascular risks of the ABL1 TKI's
5) Recognize potential autoimmune toxicities associated with the immune checkpoint inhibitors and basic management strategies for these toxicities

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The past twenty years has seen a dramatic shift in cancer therapy. While traditional chemotherapy is still a critical component of the treatment of most malignancies, molecularly targeted and immunotherapies are now routinely used in virtually all cancers. Thus, primary care physicians, hospitalists, and sub-specialists will frequently care for patients that are receiving these agents. Management of these patients is challenging as these drugs have unique side effects that differ substantially from chemotherapy. In addition, many of these therapies are oral and are taken for long durations, and, therefore, clinically important drug interactions are common. The following review will highlight the significant toxicities of the most commonly used classes of molecularly targeted and immunotherapies as well as management tips for physicians who encounter patients on these medications.

Molecularly targeted therapy

In oncology, the term "molecularly targeted therapy" refers to drugs that target or inhibit specific molecule(s) known to play a role in cancer development and proliferation. The two primary classes of agents used are monoclonal antibodies and small molecule inhibitors (designated by the suffixes "mab" and "ib," respectively). Monoclonal antibodies are engineered to be highly specific in their targeting, while the small molecule inhibitors are often "dirtier" and may affect multiple molecular targets. In many cases, these therapies are chosen based on certain biomarkers within the patient's tumor that predict for an excellent response to treatment with a specific therapy. In 2002, imatinib was one of the first molecularly targeted therapies to be FDA approved. Over the ensuing 15 years, therapies directed against dozens of targets have been developed, including an entire new class of therapy – immunotherapy. In many cases, there are now multiple agents FDA approved for a given target. It is therefore extremely challenging, if not impossible, for the average physician to keep track of all the drugs available. However, there are features unique to the most commonly used classes of molecularly targeted agents that are important for an internist caring for patients on these medications to understand.

Her-2

The gene *ERBB2* encodes for a protein most commonly designated HER-2, which is a member of the EGF family of receptor tyrosine kinases. HER-2 is overexpressed or amplified in many solid tumors, and this serves as a predictive marker for which tumors are likely to respond to HER-2 directed therapy. There are currently three FDA approved monoclonal antibodies directed against HER-2: trastuzumab, pertuzumab, and ado-trastuzumab emtansine (a monoclonal antibody against HER-2 linked to a microtubule poison) In addition, there are two oral tyrosine kinase inhibitors (TKI), lapatinib and neratinib, that are directed against both EGFR and HER-2. Trastuzumab is approved for use in the adjuvant and metastatic settings in HER-2 overexpressing breast cancer as well as in HER-2 overexpressing metastatic gastro-esophageal junction and gastric cancers. The other agents are currently only utilized in HER-2 overexpressing breast cancer.

Congestive heart failure (CHF) and asymptomatic decline in left ventricular systolic function (LVSF) are established risks of HER-2 directed therapies. The precise mechanism is debated, but it has been proposed that the HER-2 targeted antibodies prevent the formation of HER-2/HER-4 heterodimers in cardiac myocytes. In animal models, activation of these heterodimers by neuregulin-1 protects the cardiac myocytes against stress, and as a result, inhibition of heterodimer formation renders the cell more susceptible to a variety of injuries, including anthracycline induced cardiac toxicity.

The cardiac effects of the HER-2 directed agents are idiosyncratic and not dose dependent, and declines in LVSF are generally reversible if managed appropriately. Therefore, routine monitoring of LVSF is standard of care in patients receiving these drugs. The adverse cardiac effects are also potentiated by concurrent or prior use of anthracyclines. In a large review of over 11,000 breast cancer patients in adjuvant trials that included a treatment arm with trastuzumab, the incidence of CHF was 2.5% in patients receiving trastuzumab and 0.4% in the control group (RR 5.11; 90% CI 3.00 to 8.72, P < 0.00001). The incidence of decline in LVSF was 11.2% in trastuzumab patients and 5.6% in controls (RR 1.83; 90% CI 1.36 to 2.47, P = 0.0008).[1] Similar rates of CHF (0.9% to 4%) and decline in LVSF (4.4% to 16%) are seen with pertuzumab. The risk of a significant decline in LVSF with either lapatinib or ado-trastuzumab emtansine is under 5%.

In addition to targeting HER-2, both lapatinib and neratinib also inhibit the EGFR tyrosine kinase and (as will be discussed in detail below) their toxicity profile therefore includes effects such as rash and diarrhea that are commonly seen with the EGFR targeted agents.

Significant drug interactions

Dose adjustment of lapatinib is recommended when it is used concomitantly with strong CYP3A4 inducers or inhibitors.

VEGF

The VEGF pathway is an important mediator of angiogenesis, which plays a critical role in normal tissue viability, growth, and wound healing as well as in proliferation and metastasis of many tumors. Multiple drugs targeting this pathway are currently approved, including the monoclonal antibodies bevacizumab and ramucirumab, aflibercept (a decoy receptor that "traps" VEGF), and several small molecule tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib, axitinib, regorafenib, lenvatinib, cabozantinib, and vandetanib). VEGF targeted therapy is used in many malignancies including lung, ovarian, cervical, renal cell, gastric, thyroid (medullary and well-differentiated), colorectal, hepatocellular, pancreatic neuroendocrine, high-grade glioma, mesothelioma and sarcoma.

One side effect seen universally with these agents is hypertension (Figure 1).[2] The precise mechanism whereby inhibition of VEGF results in the development of hypertension is not established, but there are several viable theories developed from pre-clinical models. VEGF inhibition results in decreased production of nitric oxide resulting in vasoconstriction and increased peripheral vascular resistance.

Table 1. Incidence of hypertension with VEGF and multi-kinase inhibitors [37–53, 54•, 55]

VEGF or multi-kinase inhibitor	Therapeutic target(s)	FDA-labeled Indication(s)	Incidence of all-grade hypertension	Incidence of grade 3 and 4 hypertension
Bevacizumab	VEGF ligand	Cervical cancer, colorectal cancer, glioblastoma multiforme, non-small-cell lung cancer, ovarian cancer, renal cell cancer	22–24 %	8 %
Sunitinib	PDGFR, VEGFR, KIT, FLT3, CSR, RET	Gastrointestinal stromal tumors, pancreatic neuroendocrine tumor, renal cell cancer	15–34 %	7 %
Sorafenib	VEGF-R, PDGFR, KIT, FLT-3, RET	Hepatocellular cancer, renal cell cancer, thyroid cancer	17–29 %	4–11 %
Axitinib	VEGFR	Renal cell cancer	40 %	11–13 %
Pazopanib	VEGFR, PDGFR, FGFR, KIT, Itk, Lck, c-FMS	Renal cell cancer, soft-tissue sarcoma	36–46 %	4–7 %
Cediranib	VEGFR	None currently (being studied in recurrent ovarian carcinoma)	67 %	43 %
Regorafenib	VEGFR, FRFR PDGFR, c-KIT, REF, BRAF	Colorectal cancer, gastrointestinal stromal tumors	28–48.5 %	7–22.7 %
Cabozantinib	RET, MET, VEGFR, KIT, TRKB, FLT3, AXL, TIE-2	Thyroid cancer	32–37 %	8–15 %

Figure 1. Incidence of hypertension with the VEGF inhibitors (adapted from reference 2)

Another result of inhibition of the VEGF pathway is decreased capillary density (or rarefaction) that also leads to increased vascular resistance. Lastly, VEGF inhibition may result in produce a pre-eclampsia like picture with hypertension and proteinuria.

Regarding the management of hypertension that results from VEGF inhibition, specific dose reduction and omission recommendations are employed when significant hypertension is observed with these agents. There are, however, no prospective trials or evidence-based guidelines for the treatment of hypertension that is caused by a VEGF targeted drug. In general, it is recommended to follow standard guidelines for the management of hypertension, such as the Joint National Commission 8. There is preliminary data that the use of nitric oxide donors, such as isosorbide mononitrate and dinitrate, may be effective in refractory hypertension secondary to VEGF inhibitors, but this requires confirmation in larger prospective trials.[2]

The use of VEGF inhibitors has also been linked to thrombotic events. Given that it was the first VEGF targeted agent approved, bevacizumab has been studied most extensively. A meta-analysis of over 12,000 patients from 20 randomized trials found that the rates of all-grade and high grade arterial thrombotic events (ATE) with bevacizumab were 3.3% (2.0 – 5.6%) and 2% (1.7% - 2.5%), respectively. The RR for ATE was 1.44 (95% CI 1.08–1.91).[3] A similar analysis of venous thrombotic events (VTE) in over 6000 patients from 10 randomized trials did not find a significant association between the use of bevacizumab and VTE (odds ratio 1.14; 95% CI 0.96–1.35).[4] Regarding the VEGF TKI's, a systematic review and meta-analysis of more than 10,000 patients receiving sorafenib or sunitinib found an

incidence for ATE of 1.4% (95% CI, 1.2% to 1.6%), and a RR of ATE of 3.03 (95% CI, 1.25 to 7.37; P = .015) compared with controls.[5] The consensus opinion is that a modest, but significant, increase in ATE is associated with all of the VEGF targeted agents. While VTE have been reported with these agents, conclusive evidence for a significant association between VEGF inhibition and VTE is lacking.

Another class effect of the VEGF inhibitors is proteinuria. While the definitive pathogenesis is not established, it is thought that interruption of VEGF action on the renal endothelium is the precipitating cause. The incidence of proteinuria with VEGF inhibition ranges from 8 – 73%, but the rate of $\geq$ grade 3 proteinuria (> 3.5 grams in 24 hours) is only 3 – 5%.[6,7] Patients are generally monitored throughout treatment with urinalysis and/or a urine protein/creatinine ratio, and treatment is typically held if nephrotic range proteinuria develops. There are no specific prophylactic or treatment recommendations for VEGF induced proteinuria, though angiotensin converting enzyme inhibitors have been used in some instances.

Additional adverse effects of VEGF inhibition are an increased risk of gastrointestinal perforation (GIP) and impaired wound healing. In a large observational cohort of 1953 patients receiving bevacizumab for colorectal cancer (the BRiTE study), GIP (which included fistula formation and intra-abdominal abscess) was observed in 1.9% (95% CI, 1.3%–2.5%).[8] In the multivariate analysis, age > 65 years, an intact primary tumor and prior adjuvant radiation therapy were all independent predictors of GIP. A large meta-analysis of over 26,000 patients receiving bevacizumab from 33 randomized controlled trials including a variety of tumor types found a significantly increased relative risk of GIP with bevacizumab (RR 3.35, 95 % CI 2.35–4.79, P < 0.001).[9] A second meta-analysis that included more than 11,000 patients from 17 randomized controlled trials of bevacizumab reported a rate of GIP of 0.9% (95% CI 0·7–1·2) and a relative risk of 2.14 (95% CI 1·19–3·85; p=0·011).[10] Similar rates have been reported with aflibercept, and GIP has been reported with virtually all of the available VEGF inhibitors.

Regarding wound healing, in the BRiTE study, 23 of 521 patients (4.4%) who underwent surgery within 90 days of the last dose of bevacizumab developed a significant post-operative wound healing complication. Given the long-half lives of bevacizumab, ramucirumab, and aflibercept, current recommendations suggest that they should be held for 4-6 weeks prior to major surgery and not restarted until at least 4 weeks post-operatively, ideally once the surgical wound has completely healed. With the oral VEGF TKI's, half-lives are short and the recommendations regarding wound healing vary.

Early in the clinical development of the VEGF inhibitors, mild and severe bleeding were noted as possible side effects. In one of the first studies of bevacizumab in stage IV non-small cell lung cancer, four of 13 patients with squamous cell carcinoma had life-threatening or fatal hemoptysis, and, thus, patients with squamous histology as well as those with pre-existing hemoptysis were excluded from subsequent trials of the VEGF inhibitors in lung cancer. Mild mucocutaneous bleeding such as epistaxis is relatively common with the VEGF targeted drugs and does not require a change in therapy, but the rates of significant hemorrhage are generally low. For example, in the BRiTE study, grade 3-4 bleeding was observed in 2.2% (95% CI, 1.6%–2.9%). In addition, in two separate analyses of fatal adverse events possibly related to bevacizumab and the oral VEGF TKI's, hemorrhage was the most common fatal

adverse event with an incidence of 0.4%.[11,12] In general, patients with active bleeding or those at high risk of severe hemorrhage are excluded from treatment with the VEGF inhibitors.

Significant drug interactions

Sunitinib, sorafenib, pazopanib, lenvatinib and vandetanib can produce QT prolongation, and it is therefore recommended that concomitant use of drugs that can also prolong the QT interval be avoided. In addition, strong inducers or inhibitors of CYP3A4 may affect the activity and toxicity of axitinib and regorafenib.

EGFR

EGFR (also called HER-1) is a ligand dependent receptor tyrosine kinase that is overexpressed or mutated in a variety of solid tumors. There are currently three FDA approved monoclonal antibodies directed against EGFR (cetuximab, panitumumab, and necitumumab) as well as four oral EGFR TKI's (afatinib, erlotinib, gefitinib, and osimertinib). These agents are used in several malignancies including non-small cell lung, colorectal, pancreatic, and head and neck squamous cell cancers.

Acneiform rash is commonly seen with the EGFR inhibitors. In addition, dry skin, pruritus, folliculitis, and paronychia are frequently observed. The pathophysiology is not precisely known. However, EGFR is normally expressed in keratinocytes in the epidermis, and the effects of EGFR inhibition on the skin are dose dependent. Therefore, the cutaneous toxicity is thought to be a direct result of EGFR inhibition in the skin. The reported incidence of any grade skin toxicity ranges from 10 – 90% and $\geq$ grade 3 skin toxicity is seen in up to a 1/3 of patients in some trials. Management generally includes topical, and in severe cases, oral steroids as well as oral tetracycline derivatives. Several small randomized trials have also shown benefit with prophylactic tetracyclines in reducing the severity of acneiform rash.[13]

In addition to skin toxicity, ocular effects are also seen with these agents. In large trials of the EGFR inhibitors, the incidence of significant ocular toxicity ranges from 1 - 6%. However, this may underestimate the true incidence of eye related complaints. A retrospective review of 69 patients receiving EGFR inhibitors (primarily erlotinib and cetuximab) found that over 2/3 of patients reported symptoms related to eye toxicity, most commonly foreign body sensation (38%), dryness (32%) and itchiness (28%). Their review found that the most common eye disorders related to the EGFR inhibitors were dysfunctional tear syndrome (68%), blepharitis (64%), trichomegaly (32%) and eyelid rash/hyperemia (28%).[14] These effects are generally mild and can be managed conservatively, but rarely significant corneal abrasions or ulcers (often related to misdirected eyelashes) can occur and require prompt ophthalmology referral.

Another common side effect of the EGFR targeted drugs is diarrhea. The precise mechanism remains poorly understood, but EGFR is expressed on gastrointestinal epithelium. Mild diarrhea occurs in the majority of patients (depending on the specific agent), and $\geq$ grade 3 diarrhea can occur in 2-6% (16% with afatinib). Mild diarrhea can generally be managed with over the counter anti-diarrheals such as loperamide. Dose interruption or decrease may be required for more severe toxicity. However, the diarrhea is often self-limited, and therefore, treatment with the EGFR inhibitors can generally continue.

Cetuximab, panitumumab, and necitumumab also cause frequent hypomagnesemia. Decreased TRMP6 channel activation in the kidney that results from EGFR inhibition is thought to be the mechanism. Virtually all patients receiving these agents develop a decrease in the serum magnesium level during treatment, and ≥ grade 3 hypomagnesemia is seen in up to 27% (more often with cetuximab).[15] Oral magnesium is generally ineffective and poorly tolerated due to diarrhea. Therefore, patients typically require frequent intravenous repletion of magnesium while receiving these antibodies, and the hypomagnesemia may persist for as long as 3 months after treatment is completed. Patients receiving these drugs should have a magnesium level checked at every encounter with a provider.

Significant drug interactions

The absorption of erlotinib and gefitinib is dependent on an acidic gastric pH. In studies of healthy volunteers, the concomitant use of erlotinib and a proton pump inhibitor (PPI) reduced the maximum serum concentration and area under the curve of erlotinib by 46% and 61%, respectively. It is therefore recommended that proton pump inhibitors be avoided in patients receiving these drugs.

Erlotinib, gefitinib, and osimertinib are also major substrates of CYP3A4. Caution and careful monitoring should be considered when concurrent use of inhibitors or inducers of this enzyme are planned.

Osimertinib produces prolongation of the QT interval (QT) in a minority of patients (approximately 3%). It is therefore recommended that regular monitoring of the QT be considered when osimertinib is used with other agents that prolong the QT.

ABL1

Imatinib, an ABL1 TKI, was the first (and to date perhaps the most successful) modern targeted therapy. It was approved in 2002 to treat chronic myelogenous leukemia (CML), and eventual discovery of additional activity against the c-kit tyrosine kinase lead to expanded approval for the treatment of gastrointestinal stromal tumor. Subsequently, four additional ABL1 TKI's have been approved – dasatinib, nilotinib, ponatinib, and bosutinib. Cardiovascular adverse events have been seen to varying degrees with each of these drugs, and these effects are especially significant given that patients often remain on these medications for many years. Although there remain many unanswered questions regarding the mechanism, it appears that "off target" effects of these TKI's on the VEGF, FGF, and PDGF pathway are likely responsible for the cardiovascular toxicity (Figure 2).[16]

Kinase/TKI	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib
ABL1	100	105	83	98	101
ABL1(T315I)	93	68	9	15	100
FGFR1	79	47	0	0	101
FGFR2	95	73	3	0	100
FGFR3	83	34	1	0	101
FGFR4	3	9	8	0	98
FLT1 (VEGFR1)	97	39	5	0	101
FLT3	77	17	68	60	99
FLT4 (VEGFR3)	92	31	3	17	101
KDR (VEGFR2)	101	22	7	22	94
KIT	23	100	97	96	101
PDGFRα	77	100	98	103	103
PDGFRβ	95	99	91	93	102
SRC	96	101	5	23	102
TIE2	22	16	0	41	101

Figure 2. Percent inhibition of various tyrosine kinases by the currently approved ABL1 tyrosine kinase inhibitors at 1 micromole/L concentration (adapted from reference 16)

Imatinib is generally well-tolerated. In a large randomized trial evaluating it in CML, at 5 years of follow up, only 4% of patients had discontinued imatinib secondary to toxicity. The primary side effects are cytopenias, edema (both peripheral and periorbital), and musculoskeletal pain. In 2006, after a single institution retrospective review found 10 patients who developed left ventricular systolic dysfunction while taking imatinib, an ensuing publication of a study from that institution suggesting imatinib caused cardiomyopathy in a murine model raised concern over the cardiotoxic effects of the drug. Subsequent long-term observation of clinical trial participants on imatinib showed no increase in cardiac dysfunction when compared with the general population. In retrospect, the original clinical report linking imatinib to cardiac dysfunction was felt to be flawed, and the results of the murine study may reflect differences in cardiac physiology between mice and men or may have resulted from the exceptionally high doses of imatinib used.

As is seen with imatinib, patients on dasatinib can develop cytopenias, musculoskeletal pain, and fluid retention. However, with dasatinib, fluid retention may result in a pleural effusion. The incidence of any pleural effusion varies across studies from 5 – 28%, and the rate of clinically significant pleural effusion (grade 3/4) is reported as high as 7%. Dasatinib has also been associated with the development of pulmonary arterial hypertension (PAH). In a large randomized trial comparing imatinib and dasatinib, PAH was reported in 3% of dasatinib patients and in 0% of patients receiving imatinib. A large French registry of patients on dasatinib estimated the incidence of PAH at 0.45%. In October 2011, the US Food and Drug Administration, issued a warning regarding the cardiopulmonary effects of dasatinib and suggested that patients receiving the drug be screened prior to and during treatment, though specific

screening recommendations were not provided. Certainly, in patients who develop symptoms suggestive of PAH, dasatinib should be held, and a cardiology referral should be considered.

Nilotinib is linked to several adverse metabolic and cardiac effects. A modest degree of QT prolongation is seen in a subset of patients receiving the drug. It is therefore recommended that patients avoid other QT prolonging agents and have their EKG monitored. In addition, nilotinib may produce hyperglycemia and hyperlipidemia (including total, low-density lipoprotein, and high density lipoprotein cholesterol). In one comparative trial against imatinib, 36% of patients on nilotinib developed hyperglycemia compared with 20% on imatinib (grade 3/4 hyperglycemia in 6% versus 0%, respectively). In addition, and perhaps as a result, nilotinib is also reported to cause both cardiovascular and peripheral arterial events. The incidence varies across studies, likely due to both inconsistent reporting and varied definitions of arterial and cardiovascular toxicity. In a meta-analysis of over 2000 patients receiving nilotinib, imatinib, or no-TKI, peripheral arterial occlusive disease (PAOD) was seen in 1.3%, 0.2% and 0.6%, respectively. In addition, a 6-year follow up of a trial in patients receiving nilotinib 400 mg, nilotinib 300 mg, and imatinib reported cardiovascular events (defined as ischemic heart disease, ischemic cerebrovascular disease, PAD) in 10%, 15.9%, and 2.5%, respectively (? P value). As a result, close attention to cardiovascular risk modification and monitoring are recommended for patients on nilotinib (a proposed monitoring schedule is shown in Figure 3).

Table 3. Provisional Recommendations for Cardiovascular/Cardiometabolic Follow-Up of Patients Receiving BCR-ABL1 TKIs

Assessment	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Baseline	Follow good clinical practice				
Clinical cardiovascular assessment, including blood pressure		REC	REC	REC	REC
Fasting glucose		REC	ACI	ACI	REC
Fasting lipid panel		REC	ACI	ACI	REC
Echocardiogram		ACI	ACI*	ACI	ACI
ECG		REC†	REC	ACI	ACI
Ankle-brachial index		REC	ACI	ACI	REC
1-month follow-up					
Clinical cardiovascular assessment		REC	REC	ACI	REC
Blood pressure check		ACI	ACI	ACI	REC
3- to 6-month follow-up					
Clinical cardiovascular assessment		REC	REC	REC	REC
Blood pressure check		REC	ACI	ACI	REC
Fasting glucose		REC	ACI	ACI	ACI
Fasting lipid panel		REC	ACI	ACI	REC
Echocardiogram		ACI	ACI*	ACI	ACI
ECG		ACI†	ACI	ACI	ACI
Ankle-brachial index		REC	ACI	ACI	REC

NOTE. Practice guidelines regarding prevention of cardiovascular toxicity should be followed, including tobacco cessation counseling. In symptomatic patients or those with high cardiovascular risk, consider referral to cardiologist.
Abbreviations: ACI, as clinically indicated; ECG, electrocardiogram; REC, recommended; TKI, tyrosine kinase inhibitor.
*Low threshold for an echocardiogram in patient considered for treatment or being treated with dasatinib who has cardiopulmonary symptoms.
†ECG prior to starting, after 7 days after starting, and after each dose change (package insert).

Figure 3. Proposed cardiovascular monitoring schedule for patients on an ABL TKI (adapted from reference 16)

Ponatinib also has significant cardiovascular toxicity. In long term follow up (median 28 months) of the original study that lead to its approval, cardiovascular events were seen in 10%, cerebrovascular events

in 7% and peripheral arterial events in 7%. In addition, as was predicted by the off target VEGF receptor inhibition caused by ponatinib, 26% of patients developed hypertension. These events resulted in a temporary suspension of marketing of ponatinib in the United States and a change to the FDA label. As might be expected, patients with traditional cardiovascular risk factors (age, hypertension, diabetes, hypercholesterolemia) are at the highest risk for cardiovascular events with ponatinib. Currently, the drug carries a Black Box warning for arterial and venous occlusions, heart failure, and rare hepatotoxicity. Careful patient selection and close monitoring are therefore required when utilizing ponatinib (Figure 3).

Bosutinib is currently approved as salvage therapy for CML and can cause cytopenias and fluid retention, including pleural effusions. Grade 3/4 fluid retention is seen in up to 5% of patients. Significant cardiovascular effects have not been seen to date, but occasional hepatic and renal toxicity is reported.

Significant drug interactions

With exception of ponatinib (which is a minor substrate), the other BCR/ABL TKI's are major substrates for CYP3A4, and therefore caution should be used when combining with inhibitors and inducers of that enzyme.

Dasatinib, bosutinib, and nilotinib require acidic gastric pH for absorption, and therefore, concurrent use of proton pump inhibitors is not recommended. If required, other antacid medications (such as H2 blockers) may be considered, but their administration should be separated from the ABL TKI by at least 2 hours.

Immunotherapy

CTLA-4 and the programmed death receptor 1 (PD-1) are proteins expressed on T-cells that downregulate the T-cell response, and, as a result, these molecules have been termed "immune checkpoints." Monoclonal antibodies directed against CTLA-4 and PD-1 (or it's ligand PD L-1) restore T-cell mediated anti-tumor immunity and have been given the moniker "immune checkpoint inhibitors." Ipilimumab is the only approved anti-CTLA-4 monoclonal antibody and is currently used in melanoma. There are several monoclonal antibodies approved against PD-1 (nivolumab and pembrolizumab) and PD L-1 (atezolizumab, avelumab, and durvalumab), and these agents have demonstrated significant activity against a variety of malignancies including lung, bladder, head and neck, colorectal, Hodgkin lymphoma, melanoma, and Merkel cell carcinoma. These immunotherapy (IT) agents produce a wide spectrum of autoimmune toxicities that can affect virtually any organ. The most common of these are detailed below.

Endocrinopathies

A variety of autoimmune mediated endocrine disorders have been reported with the CTLA-4 and PD-1/PD-L1 inhibitors. The published incidence of endocrinopathies varies considerably between trials. This may be partially accounted for by variability in how these disorders were defined in individual studies. In addition, screening for these disorders was not standard, especially in early trials with the

CTLA-4 inhibitors, and therefore, the published rates of endocrine disorders may underestimate that seen in clinical practice. The median time to development of an immune mediated endocrinopathy ranges from 7 – 20 weeks after initiation of treatment with an IT agent.[17]

Thyroid disorders including thyroiditis, hypo- and hyperthyroidism occur in up to 8% of patients receiving CTLA-4 inhibitors, in up to 20% of those receiving PD-1/PD L-1 inhibitors, and in as many as 28% of patients receiving combination immunotherapy therapy (CIT) with both CTLA-4 and PD-1/PD L-1 inhibitors. Graves ophthalmopathy has also been reported. It is now standard practice to monitor TSH and free T4 levels in patients receiving these drugs. Most patients with hypothyroidism can be managed with standard thyroid hormone replacement. Those with significant hyperthyroidism and/or thyroiditis typically require referral to an endocrinologist.

Hypophysitis has also been reported in up to 17% of patients receiving the CTLA-4 inhibitors and in approximately 1% of patients receiving PD-1/PD L-1 inhibitors. Symptoms secondary to hypophysitis and resultant panhypopituitarism are non-specific and often subtle (headache, fatigue, nausea, sexual dysfunction, loss of libido) and, therefore, most centers routinely screen patients with chemistry profiles, ACTH and cortisol levels (in addition to the thyroid studies noted above) periodically during therapy with these agents. Prior to routine screening for these disorders, rare cases of adrenal crisis secondary to hypophysitis (or in some cases primary adrenalitis) were reported. If hypophysitis is suspected, immunotherapy is held, and an MRI of the brain should be performed to exclude pituitary metastasis. Typical findings of hypophysitis include enhancement and variable swelling of the pituitary. Involvement of the optic chiasm, and resultant visual symptoms, are rare. These patients also require immediate referral to an endocrinologist for confirmation of the diagnosis and management of hormone replacement. The hypophysitis will generally respond to high-dose steroids, and in many cases, immunotherapy can be resumed once the steroids are tapered and the patient is on hormone replacement.

Cutaneous effects

Cutaneous toxicity is also reported with the IT agents. It is generally seen earlier than other adverse events (median time to development is 2 – 10 weeks), although delayed onset has also been reported. The most common manifestation is a pruritic maculopapular rash that can vary in severity and extent. However, psoriasis, vitiligo, pruritus, DRESS (drug reaction with eosinophilia and systemic symptoms), Stephens Johnson, and toxic epidermal necrolysis have also been reported. In a meta-analysis of 9 randomized clinical trials with ipilimumab, the incidence of any grade and high grade rash were 24.3% and 2.4%, respectively.[18] In this analysis, the dose of ipilimumab administered and the disease being treated (melanoma versus other malignancy) did not appear to affect the incidence of rash. In a similar analysis of trials with the PD-1 inhibitors, rash, vitiligo, and pruritus were observed in 15 – 18%, 9 -10.7% and 16 – 25%, respectively.[19] Mild rash can generally be managed with topical steroids and oral anti-histamines, and immunotherapy can be continued. In patients with severe rash, immunotherapy is held, systemic steroids are administered, and dermatology referral is recommended.

Pulmonary effects

Pulmonary toxicity secondary to the CTLA-4 and PD-1/PDL-1 inhibitors has also been described. The incidence in clinical trials varies, again likely due to discrepancies in reporting, but the true incidence is felt to be less than 10%. In a single institution, retrospective review of 298 patients receiving ipilimumab, the incidence of pneumonitis was < 1%.[20] A meta-analysis of over 4500 patients treated with a PD1 inhibitor, reported rates of all grade and high grade pneumonitis of < 3% and < 1%, respectively. In addition, a multi-center review of more than 900 patients treated with anti-PD1 therapy outside of a clinical trial reported pneumonitis in 5%, with grade 3 or greater events in 1%. With CIT, the incidence ranges from 5 – 10% (2% grade 3/4). The median time to onset is approximately 3 months, but late presentations can occur. The most common symptoms are cough and dyspnea, with fever and chest pain also occasionally reported. The radiographic changes noted can vary considerably and includes organizing pneumonia (most commonly), interstitial pneumonitis like patterns, hypersensitivity-like patterns, and non-specific/mixed patterns.[21] In addition, sarcoid-like presentations have been described. Of note, new mediastinal lymphadenopathy in a patient receiving immunotherapy should be evaluated with biopsy as it may represent sarcoidosis rather than tumor progression. Similarly, there is no pathognomonic pathologic change indicative of immunotherapy mediated pneumonitis. Lymphocyte predominance on bronchoalveolar lavage is the most common finding, but eosinophilic infiltration and granulomatous inflammation have also been described. In mild cases, cessation of immunotherapy may be sufficient to produce resolution, but in more severe cases, systemic steroids and pulmonary evaluation are required.

Gastrointestinal/hepatic

The primary gastrointestinal side effects of the immune checkpoint inhibitors are diarrhea and colitis. Colitis is defined as diarrhea with bleeding or mucus, abdominal pain, or imaging findings confirming bowel inflammation. Gastrointestinal toxicity generally occurs 5 – 10 weeks after initiation of IT, but can begin at any time. Any grade diarrhea is reported in up to 33% of patients receiving the CTLA4 inhibitors, and $\geq$ 3 (an increase or more than 7 stools per day from baseline) is seen in as many as 9%. The incidence is lower with the PD1/PDL-1 inhibitors with all grade diarrhea occurring in up to 17% and $\geq$ grade 3 see in $\leq$ 3%. With CIT, as many as 44% of patients report diarrhea ($\geq$ grade 3 in 9%). Colitis is less common, and is seen 8 – 12% of patients receiving the CTLA4 inhibitors ($\geq$ grade 3 in 7-9%) and in 2-4% of patients on anti-PD-1/PDL-1 therapy ($\geq$ grade 3 in <1 – 3%).[22] Early recognition and prompt institution of treatment is critical to prevent severe, and in very rare cases life-threatening, presentations. Mild (grade 1) diarrhea can generally be managed with loperamide and/or diphenoxylate hydrochloride. In addition, stool studies for *Clostridium difficile* and other pathogens should be considered. For persistent mild symptoms, budesonide can also be employed. Immunotherapy is generally held in patients with persistent moderate symptoms or $\geq$ grade 3 presentations, and systemic steroids are utilized. If imaging is obtained, computed tomography may show thickening of the colonic wall (most often involving the descending colon) and mesenteric engorgement consistent with underlying inflammation. Flexible sigmoidoscopy or colonoscopy may be considered when there is uncertainty regarding the diagnosis but is not required in all cases. In patients with severe, steroid refractory disease, infliximab can be effective.

The immune checkpoint inhibitors can also produce an autoimmune hepatitis in a small fraction of patients. The typical onset is 6 – 14 weeks after initiation of immunotherapy, but it can occur at any point. The incidence of all grade serum aminotransferase elevations is 0 – 7% (≥ grade 3 is 0-3%) with both the CTLA4 and PD1/PD L-1 targeted agents. With CI, the incidence has been reported as high as 30% (≥ grade 3 in 19%). In patients with mild elevations (< 3x the upper limit of normal), immunotherapy can be continued with close monitoring of the liver function tests. Viral and other drug induced causes should also be considered. In those with elevations greater than 3x the upper limit of normal and no other obvious etiology, immunotherapy is generally held and systemic steroids are utilized. For severe or refractory cases, mycophenolate mofetil is recommended.[22, 23]

Additional clinical pearls

"The IMiD's"

Lenalidomide, pomalidomide, and thalidomide are immunomodulatory agents frequently used in the treatment of myeloma. Each has been linked to increased rates of venous thromboembolism (VTE), and this risk appears to be potentiated when the drugs are combined (as they frequently are) with dexamethasone. A meta-analysis of over 3000 patients receiving either thalidomide or thalidomide with dexamethasone found the relative risks of VTE to be 2.6 and 8, respectively. In addition, in a large trial comparing lenalidomide with lenalidomide/dexamethasone found the incidence of VTE was 12% with lenalidomide and 26% with the combination. Patient's now routinely receive VTE prophylaxis when taking an IMiD (generally full dose aspirin), but this does not completely eliminate the subsequent risk of clot.

CD 20

Treatment with the monoclonal antibodies directed against CD 20 (rituximab, obinutuzumab, ofatumumab and the radio-labelled CD20 monoclonal antibodies) can result in hepatitis B reactivation in patients previously exposed to the virus. Although consensus guidelines vary by organization, it is generally accepted to screen patients with hepatitis B serologies (Hepatitis B surface antigen and anti-Hep B core antibody) prior to initiation of therapy with an anti-CD20 agent. Patients found to be positive for hepatitis B surface antigen should receive anti-viral therapy, and this should continue for 6 – 12 months following completion of anti-CD 20 therapy. Those found to be positive only for the hepatitis B core antibody should either receive anti-viral prophylaxis or should have monitoring of HBV DNA and the ALT every 3 months during treatment with an anti-CD20 agent and for 6 – 12 months after completion of therapy.

Daratumumab

Daratumumab is an anti-CD38 monoclonal antibody approved for use in refractory multiple myeloma. CD38 is also expressed on red blood cells and, as a result, daratumumab interferes with blood bank serologic tests. Plasma from patients receiving daratumumab will consistently cause panreactive positive reactions in antibody screening and crossmatch compatibility testing. Most centers have established protocols to insure the blood bank is informed prior to a patient receiving daratumumab so

that a baseline type and screen and genotyping/phenotyping can be performed. However, patients may present to other facilities that are unaware that they have received daratumumab, and this may result in delays in issuing blood if transfusion is required. Importantly, daratumumab does NOT affect ABO/RhD testing, and therefore, in an emergency, ABO/RhD compatible blood can be administered, though with the potential risk of a delayed transfusion reaction.

BRAF

The BRAF inhibitors vemurafenib and dabrafenib are approved for the treatment of metastatic melanoma and lung cancer in patients whose tumors harbor activating *BRAF* mutations. Following their approval, increased rates of secondary skin tumors (squamous cell carcinomas, keratoacanthomas, skin papillomas, and hyperkeratosis) were reported in patients receiving these drugs. Though the mechanism is incompletely understood, it appears that BRAF inhibition in wild-type *BRAF* skin cells leads to increased RAF-MEK-ERK signaling that results in the production of skin tumors. Subsequent studies have demonstrated that the combination of a BRAF inhibitor with a MEK inhibitor (trametinib or cobimetinib) results in enhanced efficacy in *BRAF* mutated melanoma. In addition, as was anticipated by the proposed mechanism of tumorigenesis just discussed, the use of combination therapy with BRAF and MEK inhibitors significantly reduces, but does not completely eliminate, the risk of secondary skin tumors.

Abiraterone

Abiraterone is a CYP17 inhibitor approved for use in hormone refractory metastatic prostate cancer that leads to decreased androgen production by the adrenal glands. One unanticipated consequence of treatment with abiraterone is an ACTH mediated increase in adrenal production of aldosterone. In early studies of abiraterone, patients developed signs of hyperaldosteronism, including hypertension, hypokalemia, and edema, and it was determined that low dose prednisone (5 mg) administered twice daily with abiraterone effectively prevented this in most patients. However, in a minority of patients (and in those who are non-compliant with their prednisone), hyperaldosteronism may still occur.

Conclusion

In 2017, molecularly targeted agents are frequently utilized in oncology, and, thus, physicians in virtually every practice setting are encountering patients on these drugs. It is therefore essential for those caring for these individuals to have a basic understanding of the common side effects and important drug interactions associated with these medications. If a patient presents with serious toxicity felt to be related to a molecularly targeted agent, in almost all instances it is appropriate to hold the potential offending drug until oncology input can be obtained. This will generally not have a negative impact on the control of the underlying malignancy. Similarly, in the case of immunotherapy, if a severe autoimmune toxicity is suspected, it is appropriate to administer systemic steroids without waiting for further guidance. Vigilance and early intervention by all providers involved in the care of these patients are required to insure successful outcomes for these individuals.

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