Managing toxicities of targeted therapies

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Introduction

The therapeutic arsenal for the treatment of cancer is changing rapidly, in particular because of the development of a new class of drugs which are commonly referred to as targeted therapies. These drugs have shown efficacy in several types of cancer, and the indication for their use is increasing rapidly.

Cancer develops through a multi-step carcinogenesis process which involves genetic aberrations and deregulation of pathways. Circulating cytokines, hormones and growth factors control the proliferation, differentiation, angiogenesis, apoptosis, function and mobility of the cell. Growth factors bind to their respective receptors on the cell surface which results in the transduction of the signal to the intracellular part by tyrosine kinase proteins. Depending on the signal, a variety of processes that are relevant for cell growth and survival are initiated, such as angiogenesis, proliferation, apoptosis and metastasis.

Targeted therapies

Targeted therapies are characterised by having one or more well defined molecular targets that are relevant for carcinogenesis, cell cycle regulation, tumour progression, metastasis, tumour angiogenesis and/or apoptosis. Targeted therapies can be divided into two groups (see Table 1): the monoclonal antibodies, binding to the extracellular part of the receptor or their ligand, and the small molecules, which inhibit the tyrosine kinase activity of the intracellular part of the receptor. Current targets of monoclonal antibodies include the vascular endothelial growth factor (VEGF) or its receptor (VEGFR), the epidermal growth factor receptor (EGFR), and the epidermal growth factor receptor 2 protein (HER2/neu). Pathways/receptors affected by the tyrosine kinase inhibitors include VEGFR, EGFR, RAS/RAF/MEK/ERK, C-kit, flt-3, and the platelet-derived growth factor receptor (PDGFR).

Toxicity of targeted therapies

Table 1 provides a list of the most commonly observed or severe toxicities of selected targeted agents which are currently being used in the clinic. The aetiology of many of these side effects, and the management of these events is mainly based on empirical findings. Some of these, such as diarrhoea and nausea, may be handled as occurring by conventional cytotoxic agents. In order to minimise side effects, one should be aware that many of these agents are metabolised in the liver by the CYP3A4 cytochrome P_{450} enzyme system (Table 1). Many other drugs are substrates (metabolised in the liver by CYP3A4), inducers or inhibitors or mixed inhibitors/inducers of the CYP3A4 enzyme. Drugs metabolised by the CYP3A4 enzyme system may compete with each other, leading to increased plasma concentrations of one or both drugs. Drugs known to induce CYP3A4 levels may decrease therapeutic levels of the targeted therapy. Examples of CYP3A4 inducers are carbamazepine, dexamethasone, phenobarbital, rifamycins, and St. John's Wort. Drugs that inhibit CYP3A4 enzyme activity include cimetidine, claritromycine, cyclosporine, fluconazol, fluoxetine, omeprazole, ranitidine and grapefruit juice. For a more detailed list of CYP3A4 inducers and inhibitors see Deininger and colleagues [1]. Only a few pharmacokinetic drug interaction studies have been performed, and the preference for use of drugs without influence on the CYP3A4 enzyme in combination with imatinib, gefitinib, erlotinib, sunitinib and sorafenib is therefore mostly based on theoretical grounds.

We will discuss the management of two common side effects of targeted therapy, hypertension and skin rash.

Managing hypertension in anti-VEGF(R) therapy

The mechanism of VEGF inhibition-related hypertension is not clearly understood, but a decreased production of nitric oxide has been proposed [2].

Table 1
Selected targeted therapies and their toxicities

Generic designation	Trade name	Category, Target	Metabolised by CYP3A4	Toxicity[a]
Bevacizumab	Avastin®	monoclonal antibody, VEGF	no	hypertension (8–67%: grade 3/4: 8–18%), thromboembolism (18%, arterial thrombosis 3–4%)), pain (61–62%), headache (2–26%), dizziness (19–26%), alopecia (6–32%), dry skin (7–20%), proteinuria (36%), gastrointestinal haemorrhage (19–24%), gastrointestinal perforation (<1–4%), cardio-/cerebrovasculair arterial thrombotic events (2–4%),wound healing problems, reversible posterior leukoencephalopathy syndrome (<1%) [b]
Cetuximab	Erbitux®	monoclonal antibody, EGFR	no	malaise (48%), pain (17–28%), fever (5–27%), headache (26%), acneiform skin rash (76–90%), nail disorders (16%), hypomagnesemia (50%), nausea (29%), diarrhoea (25%), vomiting (25%), weakness (45–48%), allergic reaction (19–21%), interstitial lung disease <1%
Trastuzumab	Herceptin®	monoclonal antibody, HER2/neu	no	pain (47%), fever (36%), chills (32%), headache (26%), skin rash (18%), nausea (8–33%), diarrhoea (25%), vomiting (8–23%), weakness (42%), cough (26%), dyspnoea (22%), infusion reaction (21–40% mostly chills and fever, 1% severe), infection (20%), allergic reaction (3%) congestive heart failure (7%), ARDS or anaphylactic reaction (<1%) [c]
Imatinib	Gleevec®	tyrosine kinase inhibitor, PDGFR, C-kit	yes	fatigue (30–53%), pyrexia (15–41%), headache (27–39%), skin rash (36–53%), fluid retention (7–81%), nausea (47–74%), diarrhoea (39–70%), vomiting (21–58%), abdominal pain (30–40%), haemorrhage (24–53%), neutropenia (3–48%), hepatotoxicity (6–12%), muscle cramps (28–62%)
Gefitinib	Iressa®	tyrosine kinase inhibitor, EGFR	yes	skin rash (43–54%), acne (25–33%), dry skin (13–26%), diarrhoea (48–76%), nausea (13–18%), pruritis (8–9%)
Erlotinib	Tarceva®	tyrosine kinase inhibitor, EGFR	yes	fatigue (14–55%), headache (17%), acneiform skin rash (50–8%), pruritis (13–55%), dry skin (12–35%), diarrhoea (30–56%), anorexia (23–52%), nausea (11–33%), hyperbilirubinemia (20%), dyspnoea (21–41%)
Sunitinib	Sutent®	tyrosine kinase inhibitor, VEGFR, PDGFR, C-kit	yes	hypertension (15–28%), fatigue (42–74%), headache (13–25%), skin rash (14–38%), hyperpigmentation (30–33%), dry skin (17%), hand–foot syndrome (12–14%), diarrhoea (40–55%), nausea (31–54%), mucositis/stomatitis (29–53%), dyspepsia (46%), anorexia 31–33%), neutropenia (53%), thrombocytopenia (38%), bleeding (18–26%), LVEF decreased (10%), hypothyreoidism (4–7%), reversible posterior leukoencephalopathy syndrome (<1%) [b]
Sorafenib	Nexafar®	tyrosine kinase inhibitor,VEGFR, RAF, C-kit PDGFR	yes	hypertension (18%), fatigue (32–33%), skin rash (38–40%), hand–foot syndrome (30–35%), alopecia (27%), pruritus (19%), hypophosphataemia (45%), diarrhoea (37–43%), nausea (23%), lymphopenia (23%), neutropenia <10–18%), haemorrhage (15%), reversible posterior leukoencephalopathy syndrome (<1%)

[a] From www.uptodate.com June 2007. [b] Percentage reported with single-agent therapy.
[c] Percentages reported as part of combination chemotherapy regiments.
VEGF(R): vascular endothelial growth factor (receptor); EGFR: epithelial growth factor receptor; HER2/neu: epidermal growth factor receptor 2 protein; PDGF(R): platelet derived growth factor (receptor).

Symptomatic cardiovascular toxicity related to hypertension in studies with bevacizumab, sunitinib and sorafenib is uncommon, but serious events have been reported with low frequency (<1%) such as hypertensive crisis, cerebrovascular events, myocardinfarct and the reversible posterior leukoencephalopathy syndrome (RPLS) [3,4]. Because of this, as well as the fact that results from long-term follow-up after VEGF inhibition are not yet available, the management of hypertension is important.

A calcium channel blocker is a likely first choice to treat VEGF(R) targeting related hypertension because of its vasodilating effects. In the pivotal study in colorectal cancer by Hurwitz and colleagues [5] hypertension was controllable in all patients and no complications of hypertension were reported. Importantly, discontinuation of bevacizumab for hypertension was not required in any patient. There are no such studies with sunitinib or sorafenib, and their interactions with the CYP3A4 enzyme may pose a problem when used in combination with other drugs. Since calcium channel blockers are substrates of the CYP3A4 enzyme, amlodipin may be the drug of choice in this class of agents since it has a low interaction of CYP3A4. Angiotensin-converting enzyme inhibitors and diuretics have no interaction with CYP3A4. When beta blockers are used, atenolol is preferred due to its lack of metabolisation in the liver.

Before initiation of anti-VEGF therapy, the baseline blood pressure should be recorded as reference value. When the diastolic blood pressure increases $\geqslant 20$ mm Hg above baseline value or when blood pressure exceeds 150/100 mm Hg (grade 1 according to CTC), bevacizumab should be withheld and antihypertensive treatment should be initiated. A possible treatment plan for hypertension is as follows. In case of insufficient effect (i.e. blood pressure not below CTC grade I), one should proceed to the next step: Step 1: start amlodipin 5 mg/day (when a calcium channel blocker is contraindicated, start atenolol 50 mg/day); Step 2: increase the amlodipin dose to 10 mg/day (when calcium channel blocker is contraindicated go to step 3); Step 3: add lisinopril 5 mg/day; Step 4: increase the lisinopril dose to 10–20 mg/day; Step 5: add hydrochlothiazide 25 mg/day or start atenolol 50 mg/dag.

The decision to stop administering or decrease the dose of sunitinib or sorafenib at this moment depends on the blood pressure and possible accompanying symptoms and reaction on the treatment of the antihypertensive drugs. Bevacizumab administration is usually only resumed when blood pressure has decreased to values below CTC grade 1. Dose reductions of bevacizumab are currently not recommended. Anti-VEGF therapy should be permanently discontinued in any patient who experiences symptomatic cardiovascular toxicity resulting from hypertension.

Managing skin toxicity induced by anti-EGFR therapy

Anti-EGFR therapies (cetuximab, panitumumab, erlotinib and gefitinib) are associated with various cutaneous side-effects like rash, hair modifications, paronychial inflammation and xerosis [6]. These side-effects are the most common adverse events associated with these agents and occur in more than 50% of the patients [6]. The rash is situated primarily on the face, neck and upper torso and is characterised by inter- and intrafollicular papulopustules, and usually occurs during the first 2 weeks of treatment [7]. There appears to be a relationship with the occurrence of this toxicity and clinical efficacy.

The terminology for these skin reactions varies greatly (rash, acne, acneiform skin reaction, folliculitis, maculopapular skin rash etc).The aetiology of the skin toxicity is still unclear [6–8]. EGFR is expressed and activated in many skin cells with the strongest expression in proliferating undifferentiated keratinocytes located in the basal erpidermal layer and the outer root sheath of hair follicles [9]. EGFR inhibition disturbs the balance between proliferation and differentiation of keratinocytes [9–11]. Abnormal expression is implicated in epithelial tumour formation [12] and epidermal hyper proliferation disorders such as psoriasis [13].

No evidence-based recommendations for managing rash are currently available [7]. Emollients are advised to prevent and alleviate the skin dryness, and the rash may be covered with makeup [8]. A possible treatment plan for acneiform rash CTC grade $\leqslant 2$ is as follows. If results are insufficient one should proceed to the next step. Step 1: topical antibiotics like erythromycin, clindamycin or metronidazole; Step 2: systemic antibiotherapy with minocycline 100 mg/day; Step 3: topical retinoids (0.02% tretinoin-creme) two times/day;

In the case of a CTC grade 3 folliculitis, the EGFR inhibitor should be interrupted until CTC $\leqslant$ grade 2. If a S.aureus infection is confirmed, or a clinical diagnosis of impetigo is made, consider topical mupirocin (Bactroban^{R}). Pruritis may be treated with an oral antihistamine. For the treatment of non-folliculitis rash topical steroids (0.05% betamethasone) can be helpful [6].

Conflict of interest statement

None declared.

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