Metabolic disorders associated with the use of targeted cancer therapies

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Purpose of review
The everyday use of targeted therapies, whose mechanisms of action differ from the conventional cytotoxic agents, also causes the emergence of new toxicities as metabolic disorders about which little is known. We propose a systematic literature review of the incidence and physiopathology of targeted therapies-induced metabolic disorders and provide some management guidance.

Recent findings
In recent decades, significant breakthroughs in molecular oncology and immunology have been made. The administration of targeted therapies and immunotherapy has been associated with metabolic toxicities such as endocrine disorders, dyslipidemia, induced diabetes, and electrolytic disorders. Current data show that metabolic disorders are becoming increasingly common, but rarely life threatening and often reversible with prompt therapeutic intervention.

Summary
In the era of targeted therapies, medical oncologists should know the symptoms, carefully monitor patients for potential metabolic disorders, and manage these emerging side-effects with the help of endocrinologists and other medical specialists.

Keywords
immunotherapy, management, metabolic disorders, physiopathology, targeted therapies

INTRODUCTION

In recent decades, significant breakthroughs in molecular oncology and immunology have been made. The emergence of targeted therapies also causes the emergence of new toxicities, about which little is known. The administration of targeted therapies and immunotherapy has been associated with metabolic toxicities such as endocrine disorders, dyslipidemia, induced diabetes, and electrolytic disorders. This systematic review aims to describe the incidence, symptoms, and physiopathology of targeted therapies-induced metabolic disorders and provide some management guidance.

ENDOCRINE DISORDERS

Targeted therapies and immunotherapy are often associated with endocrine disorders such as thyroid dysfunction, hypophysitis (Table 1) [1–11,12▪], or reproductive disorders.

Tyrosine kinase inhibitor-induced thyroid dysfunction

Thyroid dysfunctions, mainly hypothyroidism, are common in patients receiving tyrosine kinase inhibitor (TKI) and can significantly alter the patient's quality of life, but are usually easily managed when diagnosed. The diagnosis is based on thyroid-stimulating hormone (TSH), T3, and T4 assessment [13].

Hypothyroidism is described in 11–70% of patients receiving TKI targeting vascular endothelial growth factor receptors [1–8]. Thyroid dysfunction may be subclinical or clinical [14]. Many symptoms of hypothyroidism such as fatigue and constipation are common in patients with cancer, and it can be difficult to distinguish between symptoms attributable to the underlying malignancy and those due to anticancer or supportive treatments [13]. Two types of hypothyroidism have been described as a result of treatment with TKIs. The first type of thyroid disturbance seen with TKIs, mainly sunitinib, is

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KEY POINTS

- Targeted therapies-induced metabolic disorders such as thyroid dysfunctions, immune-related hypophysitis, glycemic disorders, dyslipidemia, and electrolyte disorders are becoming increasingly common and should be closely monitored during treatment with targeted therapies.
- Targeted therapies-induced metabolic disorders are generally not acutely toxic and are often reversible with therapeutic intervention.
- Clinical evaluation and biological monitoring should be done carefully in collaboration with an endocrinologist and other medical specialists.

hypothyroidism in patients with previously normal thyroid function [13]. The second is the recurrence of hypothyroidism in patients with preexisting thyroid dysfunction. This effect is seen mainly with imatinib, sorafenib, and, more recently, vandetanib [6,15–17].

Hyperthyroidism is a much less-common effect, often preceding hypothyroidism, and is characterized by hypermetabolism symptoms such as diarrhea, sudden weight loss, and hyperthermia [18].

The most likely explanation for TKI-induced hypothyroidism is that TKI alters thyroid blood flow and then induces hypovascular destructive thyroiditis. This causes transient hyperthyroidism followed by a durable hypothyroidism [18]. Other potential explanations are impairment of iodine absorption and induction of the immune system by antithyroid peroxidase antibodies [19].

In the case of worsening preexisting hypothyroidism, an increase in TSH is likely attributable to increased clearance of thyroid hormone. TKI activates type 3 deiodinase, which inactivates both T3 and T4 [13].

For patients treated with TKIs and not receiving thyroid hormone replacement, completion of a pretherapeutic thyroid assessment and regular TSH monitoring during the first round of treatment is recommended [3,13,20]. The occurrence of thyroid dysfunction does not require any treatment discontinuation in the absence of severe symptoms, but an endocrinologist expert's advice should be considered [13].

In cases of hypothyroidism, replacement therapy is considered only in the case of symptomatic or

Table 1. Incidence of endocrine disorders under targeted therapies and immunotherapy

Authors, year [reference]	Study design	Type of targeted therapy	No. of patients	Tumor type	Hypothyroidism, *n* (%)	
					All grade	Grade 3/4
Desai *et al.*, 2006 [1]	Observational prospective	Sunitinib	42	GIST	22 (52%)	–
Mannavola *et al.*, 2007 [2]	Observational prospective	Sunitinib	24	GIST	17 (70%)	–
Wolter *et al.*, 2008 [3]	Observational prospective	Sunitinib	59	RCC/GIST	36 (61%)	–
Clement *et al.*, 2008 [4]	Observational prospective	Sorafenib	38	RCC	7 (18.4%)	–
Schmidinger *et al.*, 2011 [5]	Observational prospective	Sunitinib or sorafenib	87	RCC	30 (34%)	–
Wells *et al.*, 2012 [6]	III	Vandetanib	231	MTC	(49.3%)	
Motzer *et al.*, 2013 [7]	III	Axitinib	359	Advanced or M+ RCC	72 (20%)	1 (<1%)
Motzer *et al.*, 2013 [8]	III	Pazopanib	554	Advanced or M+ RCC	67 (12%)	0 (0%)
Motzer *et al.*, 2013 [8]	III	Sunitinib	548	Advanced or M+ RCC	133 (11%)	2 (<1%)

Authors, year (reference)	Study design	Type of targeted therapy	No. of patients	Tumor type	Hypophysitis, *n* (%)	
					All grades	Grade 3/4
Hodi *et al.*, 2010 [9]	III	Ipilimumab	131	Melanoma M+	10 (7.6%)	5 (3.8%)
O'Day *et al.*, 2010 [10]	II	Ipilimumab	155	Melanoma M+	9 (5.8%)	4 (2%)
Weber *et al.*, 2009 [11]	I/II	Ipilimumab	57	Melanoma M+	6 (11%)	3 (5%)
Faje *et al.*, 2014 [12▪]	Retrospective	Ipilimumab	154	Melanoma M+	17 (11%)	–

GIST, gastrointestinal stromal tumor; M+, metastatic; MTC, medullary thyroid cancer; RCC, renal cell carcinoma.

severe hypothyroidism [21], with a TSH cutoff of up to 10 μIU/ml required for initiation of hypothyroidism treatment [22]. Uncertainty regarding the role of thyroid hormones in tumor growth led Garfield *et al.* [23] to caution against the use of thyroid replacement treatment. Indeed, some data have shown a protective role of hypothyroidism in these patients and some of the beneficial effect of sunitinib may be due to thyroid hormone depletion. Wolter *et al.* [3] showed that progression-free survival was better in patients who had hypothyroidism (10.3 months) compared with patients who remained euthyroid (3.6 months) in renal cell carcinoma or gastrointestinal stromal tumor patients receiving sunitinib. In another study, development of subclinical hypothyroidism was identified as a predictor of survival in multivariate analysis [5].

For patients initiating imatinib, sorafenib, or sunitinib therapy and receiving exogenous levothyroxine, Hamnvik *et al.* [13] recommends TSH pretreatment followed by monitoring of TSH every 4 weeks and appropriate adjustment of the levothyroxine dose. For imatinib, they suggest that it is worth considering empirically doubling the dose of levothyroxine on initiation of therapy [13]. In cases of hyperthyroidism with thyrotoxicosis, treatment with β-blockers with or without a corticosteroid should be considered but still after seeking advice from an endocrinologist [13].

Immune-related endocrine disorders due to anti-cytotoxic T-lymphocyte-associated protein 4 treatment

Treatment with the fully human anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) monoclonal antibody ipilimumab is commonly associated with the onset of immune-related adverse events and may include hypophysitis, hypopituitarism, hypothyroidism, and adrenal insufficiency and more rarely gonadotropin insufficiency [24].

Immune-related hypophysitis occurs in 7–11% of patients treated with ipilimumab [9–11,12▪]. Clinical signs usually develop after 6 weeks of treatment [25], and symptoms include fatigue, headache, memory difficulties, dizziness, vision changes, and constipation. When suspected, a complete workup, including serum potassium, sodium, morning cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, insulin-like growth factor 1, and free T4 dosage, as well as brain MRI to exclude brain metastases, is mandatory [24].

Recently, some evidence has indicated that ipilimumab-induced immune-related adverse events may be associated with clinical benefit. It was demonstrated that the occurrence of an immunological side-effect ranging from grades 1 to 4 was significantly associated with the probability of response to treatment in patients with metastatic melanoma [12▪,26,27].

The most likely mechanism is that CTLA4 blockade removes CTLA4-mediated protection from autoimmunity, and it is responsible for a large spectrum of autoimmune-inflammatory side-effects [24].

Before treatment, a blood sample should be taken to determine baseline status of corticotrope, gonadotrope, and thyrotrope hormones via morning serum cortisol, adrenocorticotropic hormone, free T3, free T4, TSH tests, and, if possible, a cosyntropin stimulation test, in addition to testosterone testing in males and FSH and LH in women as well as a clinical chemistry profile in all patients [27]. Thyroid function tests and clinical chemistry profile should also be assessed before each dose [27].

For symptomatic panhypopituitarism and for any grades 3–4 endocrinopathy, the ipilimumab dose should be held and an initial dose of methylprednisolone 1–2 mg/kg intravenously should be given. It remains unclear whether higher dosages of glucocorticoids are superior to physiological replacement regimens in the initial management of immune-related panhypopituitarism [12▪]. This should be followed by 1–2 mg/kg prednisone orally once per day with gradual tapering over 4 weeks and replacement of appropriate hormones as the steroid dose is reduced. If signs of adrenal crisis occur, administration of intravenous corticosteroids with mineralocorticoid activity is required [27]. Ipilimumab may be resumed thereafter after resolution to grade 1 or 2 toxicity but is not recommended in more severe cases [25]. Consultation with an endocrinologist is appropriate [27].

Hypogonadism and crizotinib

Recently, Weickhardt *et al.* [28,29] reported that crizotinib, a TKI active against anaplastic lymphoma kinase (ALK), MET, and ROS1, reduced total testosterone to below the lower limit of normal in two observational studies of 19 and 32 male patients, respectively, treated with the drug, with most total testosterone levels below the lower limit of normal (100 and 84%, respectively). Low testosterone in patients with cancer has been correlated with fatigue, sexual disinterest, and decreased quality of life [30].

Crizotinib led to a decrease in total and free testosterone levels but primarily in both FSH and LH, suggesting a central effect of crizotinib on the hypothalamic–pituitary axis [29] through inhibition of its two main targets, ALK and MET, which

are both expressed in the brain [31]. Interestingly, both of these receptors are also expressed in the testes. Because in some crizotinib-treated patients FSH and LH levels can exceed the upper limit of normal, it is hypothesized that an additional, direct gonadal effect of crizotinib probably exists [29].

Until further data emerge, men starting crizotinib should have baseline testosterone levels determined in an early morning blood sample [30]. Weickhardt *et al.* [29] recommend tracking free or total/free testosterone levels in all male patients treated with crizotinib and referring those with low levels to an endocrinologist for discussion of the pros and cons of replacement therapy but with no recommendation to change the crizotinib dosage.

Other tyrosine kinase inhibitor-induced reproductive disorders

TKIs inhibit proteins with known roles in gonadal development [e.g., platelet-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR)], suggesting that they may have an adverse impact on fertility; however, data regarding the effects of TKIs on gonadal function and subsequent fertility are lacking and future long-term evaluations are required [32]. Providing recommendations for strategies to preserve fertility at the time of diagnosis is advised.

GLUCOSE METABOLISM DISORDERS

Targeted therapies are often associated with glycemic disorders mostly easily manageable and partly explained by the involvement of the PI3K–AKT–mTOR pathway and the PDGFR pathway (Table 2) [8,33–35,36▪,37–40].

Hyperglycemia

Hyperglycemia is defined as an abnormally high blood glucose level. Hyperglycemia symptoms include polyuria, polydipsia, fatigue, blurred vision, weight loss, headache, and concentration difficulties [41]. Hyperglycemia has been anticipated as a side-effect of PI3K–AKT–mTOR pathway inhibitors based on the role of the pathway in regulating insulin signaling. In patients treated with everolimus or temsirolimus for renal cell carcinoma in a metastatic setting, hyperglycemia was reported in 50–57% and 12.5% of patients, respectively [33,34,39]. In breast cancer, 9–17% hyperglycemia was reported in two recent phase III trials with everolimus [36▪,37]. Interestingly, grade 1 hyperglycemia was also commonly observed in patients treated with pazopanib (43%) [33–35,36▪,37–39].

Hyperglycemia observed during mTOR inhibitor treatment may be partly explained by the involvement of the PI3K–AKT–mTOR pathway in various metabolic pathways, including those related to insulin. Huffman *et al.* [42] demonstrated *in vitro* that the effects of insulin were abolished in the presence of a PI3K and rapamycin inhibitor. Although the exact mechanism of the metabolic derangements is not entirely clear, one possibility is that physiological adaptation to pathway inhibition partially compensates for the disrupted insulin–glucose regulatory axis [43].

Recent data suggest that the PDGFR pathway has an important role in carbohydrate metabolism. The exact mechanism is not yet clear but could explain the disturbance in carbohydrate metabolism during pazopanib treatment [44].

Monitoring of fasting serum glucose is recommended before the start of targeted therapies and periodically thereafter. Optimal glycemic control should be achieved before initiating therapy with an mTOR inhibitor, and the patient should be made aware of symptoms that may develop. For patients with grade 1 hyperglycemia, no treatments or dose modifications are recommended [45]. Patients with grade 2 or higher hyperglycemia should be treated according to the American Diabetes Association and European Association for the Study of Diabetes consensus algorithm [46]. In the case of grade 3 hyperglycemia, treatment should be interrupted and resumed at a reduced dose. If grade 4 hyperglycemia occurs or a life prognostic is engaged, treatment should be permanently discontinued [47].

Hypoglycemia

A blood glucose-lowering effect in patients has been described for some TKIs. The first symptoms to appear are autonomic symptoms, consisting of palpitations, tremor, and anxiety. Neuroglycopenic symptoms include hunger, sweating, and paresthesia [48]. A retrospective study of blood glucose concentrations in 17 diabetic and 61 nondiabetic patients treated with TKIs including imatinib, dasatinib, sorafenib, and sunitinib showed statistically significant but modest decreases in mean blood glucose, which were reversible in almost all cases. Forty-seven percent of patients with diabetes were able to discontinue their diabetes medications while on a TKI [40]. Studies have shown that sunitinib and pazopanib can induce hypoglycemia, especially in diabetic patients treated with oral antidiabetic agents [49–51]. In two prospective randomized trials, hypoglycemia was reported in 15–18% of patients on pazopanib and 10% of patients on sunitinib [8,38].

The mechanism underlying the hypoglycemic effect of these drugs is unclear. Some preclinical studies have shown that the PDGFR pathway may

Table 2. Incidence of hyperglycemia/hypoglycemia under targeted therapies

Authors, year [reference]	Study design	Type of targeted therapy	No. of patients	Tumor type	Hyperglycemia, *n* (%)	
					All grades	Grade 3/4
Motzer *et al.*, 2008 [33]	III	Everolimus	269	RCC	135 (50%)	31 (12%)
Motzer *et al.*, 2010 [34]	III	Everolimus	274	RCC	156 (57%)	41 (15%)
Ellard *et al.*, 2009 [35]	II	Everolimus + exemestane	49	BC ER + HER2−	27 (55%)	2 (4%)
Beck *et al.*, 2014 [36▪]	III	Everolimus + exemestane	100	BC ER + HER2−	25 (17%)	8 (8%)
André *et al.*, 2014 [37]	III	Everolimus + vinorelbine + trastuzumab	280	BC HER2+	25 (9%)	6 (2%)
Sternberg *et al.*, 2013 [38]	III	Pazopanib	290	Advanced or M+ RCC	120 (43%)	2 (<1%)
Hudes *et al.*, 2007 [39]	III	Temserolimus	208	RCC	26 (12.5%)	1 (<1%)

Authors, year [reference]	Study design	Type of targeted therapy	No. of patients	Tumor type	Hypoglycemia, *n* (%)	
					All grades	Grade 3/4
Motzer *et al.*, 2013 [8]	III	Pazopanib	548	RCC M+	83 (15%)	2 (<1%)
Sternberg *et al.*, 2013 [38]	III	Pazopanib	290	Advanced or M+ RCC	50 (18%)	1 (<1%)
Agostino *et al.*, 2011 [40]	RS	Sunitinib, sorafenib, dasatinib, imatinib	78	–	(8.4–37.9%)	–
Motzer *et al.*, 2013 [8]	III	Sunitinib	541	RCC M+	57 (10%)	3 (<1%)

BC, breast cancer; HER2, human epidermal growth factor 2; M+, metastatic; RCC, renal cell carcinoma; RS, retrospective.

have a critical role in glycemic control, partly explaining the disturbances in glucose metabolism during treatment with TKIs targeting the PDGF pathway [44].

It is important to be aware of the potential dangers of hypoglycemia with the use of these agents and provide glycemia monitoring in diabetic patients to prevent the occurrence of severe hypoglycemia [51]. In some cases, diabetes medication may need to be reduced at the start of TKI therapy in order to avoid symptomatic hypoglycemia [40].

DYSLIPIDEMIA

Hyperlipidemia is very common with mTOR inhibitors [52] with an estimated prevalence of up to 81% (Table 3). Hypertriglyceridemia results in a significant risk of acute pancreatitis, whereas increased levels of cholesterol lead to increased cardiovascular risk [53].

The physiopathology by which mTOR inhibitors cause dyslipidemia may involve impaired clearance of lipids from the bloodstream as opposed to increased hepatic synthesis via stimulation of insulin-stimulated lipoprotein lipase [43,54].

A complete lipid profile must be performed prior to initiating mTOR inhibitor treatment and should be repeated every 6 weeks during treatment. Grades 1–2 dyslipidemia do not require any dose modification, but lipid-lowering therapy and increased surveillance should be introduced. In the case of grade 3 toxicity, treatment should be temporarily interrupted and resumed at a reduced dose (50%). In the case of grade 4 toxicity, treatment should be discontinued. The conventionally used cholesterol-lowering treatments are statins, anion-exchange

Table 3. Incidence of dyslipidemia during targeted therapies

Authors, year [reference]	Study design	Type of targeted therapy	No. of patients	Tumor type	HyperChT, *n* (%)		HyperTG, *n* (%)	
					All grades	Grade 3/4	All grades	Grade 3/4
Motzer *et al.*, 2008 [33]	III	Everolimus	269	RCC	205 (76%)	9 (3%)	191 (71%)	2 (1%)
Motzer *et al.*, 2010 [34]	III	Everolimus	274	RCC	210 (77%)	10 (4%)	200 (73%)	<1%
Ellard *et al.*, 2009 [35]	II	Everolimus + exemestane	49	BC ER + HER2−	40 (81%)	0	22 (44%)	0
Hudes *et al.*, 2007 [39]		Temserolimus	208	RCC	24 (11%)	1 (<1%)	–	–
André *et al.*, 2014 [37]	III	Everolimus + vinorelbine + trastuzumab	280	BC HER2+	–	–	22 (8%)	2 (<1%)

BC, breast cancer; HER2, human epidermal growth factor 2; hyperChT, hypercholesterolemia; hyperTG, hypertriglyceridemia; RCC, renal cell carcinoma.

Table 4. Incidence of main electrolyte disorders under targeted therapies

Authors, year [reference]	Main symptoms	Study design	Type of targeted therapy	No. of patients	Tumor type	Hypophosphatemia, *n* (%)	
						All grades	Grade 3/4
Sternberg *et al.*, 2013 [38]	Encephalopathy, congestive heart failure, ileus, rhabdomyolysis, intravascular hemolysis, and hypocoagulability	III	Pazopanib	290	Advanced/M+ RCC	100 (36%)	15 (5%)
Motzer *et al.*, 2013 [8]		III	Pazopanib	554	Advanced/M+ RCC	193 (36%)	24 (4%)
Escudier *et al.*, 2007 [56]		III	Sorafenib	902	Advanced/M+ RCC	405 (45%)	144 (16%)
Motzer *et al.*, 2008 [33]		III	Everolimus	269	Advanced/M+ RCC	87 (32%)	12 (4%)
Motzer *et al.*, 2013 [8]		III	Sunitinib	548	Advanced/M+ RCC	57 (11%)	3 (<1%)
Rini *et al.*, 2011 [57]		III	Axitinib	359	Advanced/M+ RCC	43 (13%)	6 (2%)
Rini *et al.*, 2011[57]		III	Sorafenib	355	Advanced/M+ RCC	158 (50%)	51 (16%)

Authors, year [reference]	Main symptoms	Design	Type of TKI	*n*	Tumor type	Hypokalemia, *n* (%)	
						All grades	Grade 3/4
Miller *et al.*, 2012 [58]	Digestive, muscular, and cardiac disorders	IIb/III	Afatinib	390	NSCLC M+	34 (9%)	11 (2.8%)
Sternberg *et al.*, 2013 [38]		III	Pazopanib	290	Advanced/M+ RCC	28 (10%)	5 (2%)

Authors, year [reference]	Main symptoms	Design	Type of TKI	*n*	Tumor type	Hyperkalemia, *n* (%)	
						All grades	Grade 3/4
Hutson *et al.*, 2010 [59]	Digestive, muscular, and cardiac disorders	II	Pazopanib	225	Advanced/M+ RCC+	59 (26%)	11 (5%)

Authors, year [reference]	Main symptoms	Design	Type of TKI	*n*	Tumor type	Hyponatremia, *n* (%)	
						All grades	Grade 3/4
Riechelmann *et al.*, 2008 [60]	Nausea and vomiting, headache and confusion, and cerebral edema leading to intracranial hypertension	Observational prospective	Sorafenib	58	Advanced/M+ RCC	7 (12%)	–
Sternberg *et al.*, 2013 [38]		III	Pazopanib	290	Advanced/M+ RCC	92 (33%)	16 (5%)

Authors, year [reference]	Main symptoms	Design	Type of TKI	*n*	Tumor type	Hypocalcemia, *n* (%)	
						All grades	Grade 3/4
Sternberg *et al.*, 2013 [38]	Muscle disorders with risk for laryngeal spasm	III	Pazopanib	290	Advanced/M+ RCC	96 (35%)	8 (2.7%)
Motzer *et al.*, 2008 [33]		III	Everolimus	269	Advanced/M+ RCC	46 (17%)	0
Rini *et al.*, 2011 [57]		III	Sorafenib	355	Advanced/M+ RCC	188 (59%)	5 (2%)
Rini *et al.*, 2011 [57]		III	Axitinib	359	Advanced/M+ RCC	132 (39%)	4 (1%)

Authors, year [reference]	Main symptoms	Design	Type of TKI	*n*	Tumor type	Hypomagnesemia, *n* (%)	
						All grades	Grade 3/4
Sobrero *et al.*, 2008 [61]	Arrhythmia, constipation, neurological disorders such as facial paresthesias, cramps and muscle hypotonia, tremor, and seizures	III	Irinotecan, cetuximab	638	CRC M+	91 (33.8%)	95 (3.3%)
Jonker *et al.*, 2007 [62]		III	Cetuximab	288	CRC M+	138 (48%)	15 (5%)
Hecht *et al.*, 2009 [63]		III	Folfox, bevacizumab, panitumumab	407	CRC M+	115 (28%)	20 (4%)
Hecht *et al.*, 2009 [63]		III	Folfiri, bevacizumab, panitumumab	111	CRC M+	34 (31%)	5 (5%)
Motzer *et al.*, 2013 [8]		III	Pazopanib	554	Advanced/M+ RCC	125 (23%)	1 (<1%)
Motzer *et al.*, 2013 [8]		III	Sunitinib	548	Advanced/M+ RCC	128 (24%)	7 (1%)

BC, breast cancer; CRC, colorectal cancer; HER2, human epidermal growth factor 2; M+, metastatic; NSCLC, nonsmall cell lung cancer; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

resins in cases of elevated cholesterol, and nicotinic acid or fibrate in cases of elevated triglycerides [53]. Lipid-lowering drugs can have drug interactions such as those between enzyme inducers and cytochrome P450 3A4-substrate statins. Knowledge of the pharmacokinetic and pharmacodynamic properties of lipid-lowering drugs and their interaction mechanisms helps to avoid adverse interactions without compromising the therapeutic benefits [55].

ELECTROLYTE DISORDERS

Electrolyte disorders occurring during treatment with targeted therapies are quite common, easily reversible with treatment, but can also cause severe complications and can negatively alter quality of life. The most frequently reported symptoms and causes of dyskalemia, hypophosphatemia, hypocalcemia, hypomagnesemia, and hyponatremia are shown in Table 4 [8,33,38,56–63].

Little is known about the exact mechanism causing dyskalemia, hyponatremia, and hypocalcemia. It may be somehow related to TKI-induced gastrointestinal toxicity or nephrotoxicity [64,65]. Management is mainly symptomatic [21]. More data are available regarding hypophosphatemia and hypomagnesemia.

Hypophosphatemia

Hypophosphatemia occurs in 11–50% and in about 30% of patients receiving TKI targeting vascular endothelial growth factor receptors and everolimus, respectively (Table 4). The kidneys play a critical role in the maintenance of phosphate homeostasis. Hypophosphatemia may be partly explained by targeted therapies-induced proximal tubule dysfunction and urinary phosphate loss [66,67]. Management is symptomatic and consists of the correction of the observed disorder. Intravenous phosphate is appropriate in an acute setting [68]. For management of chronic hypophosphatemia, careful replacement with phosphate and calcium may be required [68].

Hypomagnesemia

Hypomagnesemia typically develops during treatment with a TKI targeting EGFR such as cetuximab and panitumumab (Table 4). The first prospective magnesium concentration measurement study was reported by Tejpar *et al.* [69] in a cohort of 98 patients with colorectal cancer treated with EGFR-targeting antibodies. Ninety-seven percent of patients had decreasing serum magnesium concentrations during EGFR-targeting treatment compared with baseline measurements, which were mostly reversible after treatment discontinuation.

The most convincing explanation of this effect is that blocking the EGFR-signaling pathway disrupts the active transport of extracellular magnesium in the kidney [70]. Management of hypomagnesemia was nicely established by Fakih [71]. For patients with grade 2 hypomagnesemia, weekly intravenous replacement is preferred.

General monitoring

General monitoring includes performing an initial assessment and regular monitoring of electrolyte levels throughout the treatment. Bimonthly chemistry profile dosing is usually recommended during the first 3 months of treatment and then monthly until treatment discontinuation. Management is mainly symptomatic and interruption of cancer treatment is rarely justified [21].

CONCLUSION

In the era of targeted therapies, metabolic disorders are becoming increasingly common and should be monitored closely during treatment. Metabolic disorders are generally not acutely toxic and are often reversible with therapeutic intervention. Clinical evaluation and biological monitoring should be done carefully in collaboration with an endocrinologist and other medical specialists.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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