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Sunitinib-induced asthenia: from molecular basis to clinical relief

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Abstract
Asthenia-fatigue syndrome (AFS) is defined as a persistent, subjective sense of tiredness related to cancer or its treatment and greatly impacts quality of life among cancer patients. All tyrosine kinase inhibitors, but especially sunitinib, may induce AFS. The reason for sunitinib-induced AFS is not yet well understood. Adverse events caused by sunitinib associated with AFS may include anemia, hypothyroidism, nausea and vomiting. However, AFS is also reported when active treatment with sunitinib is ongoing, and no other relevant adverse event can justify it. The molecular mechanisms by which sunitinib triggers AFS remain elusive. Sunitinib displays multiple off-target tyrosine-kinase interactions and competitively inhibits multiple proteins through the blockade of their ATP-binding sites. The broad spectrum of kinases inhibited may play a key role not only in terms of activity but also in terms of toxicity induced by sunitinib. This study considered different clinical observations and current metabolic and pharmacological knowledge, leading to hypotheses regarding which molecular mechanisms may be involved in sunitinib-induced AFS in cancer patients. Deeper knowledge of the molecular mode of action of sunitinib may lead to improved optimization of its clinical use.

Keywords:
Asthenia; Cancer; Energy; Sunitinib; Tyrosine kinase inhibitors

Introduction

Asthenia-fatigue syndrome (AFS), one of the most common symptoms experienced by cancer patients, consists of poor endurance and impaired motor and cognitive function. The National Comprehensive Cancer Network (NCCN) defines fatigue as "a persistent, subjective sense of tiredness related to cancer or its treatment that interferes with usual functioning."[1] To describe fatigue, health professionals may use terms such as asthenia, lassitude, prostration, lack of energy and weakness. Cancer patients may describe AFS by saying that they feel tired, weak, exhausted, heavy or slow.

Cancer patients treated with different tyrosine-kinase inhibitors, including sunitinib, experience AFS as a common side effect. Sunitinib-associated AFS is believed to be related to the presence of anemia, hypothyroidism and metabolic disturbances induced by tyrosine kinase inhibitors. However, fatigue is usually found in the absence of low hemoglobin or thyroid hormone levels. Little is known about the molecular mechanisms that drive this symptom.

The Importance of Asthenia in Cancer Patients

Asthenia is a multifactorial syndrome that dramatically affects the to quality of life in patients with advanced cancer. The impact of asthenia in those patients was clearly shown in a smart study conducted by The Fatigue Coalition in 1997, in which it was shown that asthenia affects a patient's daily life more adversely than cancer-related pain (61 vs. 19%, respectively).[2] Furthermore, asthenia is present in nearly all patients with advanced-stage tumors.[3] The asthenia found in cancer patients may be due to cytokines secreted by the tumor, adverse events derived from anticancer treatments, hyporexia/cachexia, mood abnormalities, such as depression or reduced levels of circulating hormones (e.g., hypogonadism and hypothyroidism).[4]

Although numerous attempts to relieve the symptoms of asthenia with various drugs have occurred over the last two decades, only exercise has effectively improved asthenia in patients with cancer.[5] Currently, no study has tested drug effectiveness related to cancer-related asthenia. Recently, methylphenidate was proven to be no more effective than placebo as palliative treatment for cancer-related fatigue.[6] The management of asthenia remains an unmet need in clinical daily practice and is limited to correcting the hormonal or blood count parameters.

The lack of effective pharmacological treatments for asthenia implies that this adverse event should be avoided whenever possible.

Molecular Mechanism of Action for Sunitinib

Sunitinib is a multitargeted tyrosine-kinase inhibitor designed to inhibit various receptor tyrosine kinases (RTKs), including vascular endothelial growth factor receptor (VEGFR) types-1, -2 and -3, platelet-derived growth factor receptors (PDGFRα and PDGFRβ), and the stem cell factor receptor KIT, FLT3 and RET, when administered at doses in the nanomolecular range.[7-9] Sunitinib is characterized by a molecular similarity to ATP; therefore, sunitinib molecules compete with ATP for binding to the intracellular ATP-binding pocket of the tyrosine-kinase receptors that trigger the molecular routes that lead to functional effects such as cell growth, tumor proliferation, angiogenesis, etc.[10] Most, if not all, protein kinases identified in the human genome have an ATP-binding site.[11] Due to the similarity to ATP, sunitinib not only binds to these previously mentioned receptors but also binds to at least 68 other kinases. The clinical importance of inhibiting off-target kinases such as JAK1, the calcium/calmodulin protein kinases, or several cyclin-dependent kinases (CDKs) is not yet known, but it is believed that some toxicity may be induced by this inhibition.[12]

A deeper knowledge of the activity and adverse events induced by off-target kinases will help us to more effectively select patients for sunitinib treatment in clinical practice.[13]

The Incidence and Severity of Asthenia in Sunitinib Treated Patients and Related Clinical Management

The incidence of asthenia or fatigue is a very common symptom to anti-angiogenic therapies for which no specific cause can usually be identified. In a retrospective analysis performed in two tertiary oncology centers in the USA for all patients with metastatic renal cell carcinoma treated out of a clinical trial showed that incidence of fatigue was 53%, 40% and 40% at any grade and 11%, 10% and 4% considering only at grade 3/4 for sunitinib, sorafenib and bevacizumab respectively.[14] Asthenia, together with hypertension and skin toxicity, were the dose limiting toxicities found in phase I trials with sunitinib administered as a single agent. In these early studies, grade 3 or 4 asthenia occurred mostly when the plasma levels of sunitinib increased to levels over 100 ng/ml.[15] Renal cell carcinoma patients treated with sunitinib in either phase II or phase III trials experienced different toxicities and adverse events, including asthenia, dermatologic disturbances, intestinal toxicity and hypertension. Among these side effects, asthenia is the most common event associated with sunitinib administration (64–68% at any grade; 16% grade 3 or 4), although its intensity and effect on quality of life varied.[16] Fatigue typically occurs 2–3 weeks after the initiation of treatment and may intensify during weeks 3 or 4, sometimes representing a recurrent problem, although severity appears to vary throughout treatment.

Several treatable and non-treatable factors may contribute to fatigue and weakness in patients with renal cell carcinoma (RCC). These factors include pain, emotional distress, anemia, sleep disturbance, nutrition, hypophosphatemia and hypomagnesemia, activity levels, hypothyroidism and comorbid conditions. Fatigue and asthenia may also be caused or exacerbated by underlying dehydration, and care should be taken to ensure patients have adequate fluid intake. Patients at high risk of fatigue or asthenia include elderly, frail or obese patients and those with a large tumor burden.

Prior to treatment, patients should be counseled on what to expect from treatment, and psychological support should be provided when feasible. During the first 2 to 3 cycles of treatment, it is important to provide close support to counsel and motivate the patient on how to cope with fatigue and weakness. If quality of life is compromised because of fatigue or asthenia, the dose of sunitinib should be reduced. During every cycle, patients should be monitored for anemia, hypothyroidism and depression, and the appropriate treatment should be initiated. In patients with symptoms suggestive of hypothyroidism, the laboratory monitoring of thyroid function and subsequent treatment according to standard medical practice are recommended. Thyroid function should also be monitored in patients with severe asthenia and in those with a reduction of 20% in Karnofsky performance status.[17] The half life for the appearance of asthenia is approximately 8 d, and the maximum level of asthenia is reached after one cycle of treatment with sunitinib.[18]

The origin of sunitinib-associated asthenia is difficult to explain. One possible explanation is that sunitinib may cause thyroid dysfunction[19] and, as a consequence, anemia, which could in turn contribute to fatigue in patients.

Influence of Asthenia in Clinical Outcome

Sunitinib is approved multinationally for the treatment of advanced renal cell carcinoma (RCC), metastatic gastrointestinal stromal tumors (GIST) after progression or intolerance to imatinib, and has recently received the approval by the European Medicine Agency (EMA) for the treatment of patients with advanced pancreatic islet cells neuroendocrine tumors (pNETs).[20-22] Houk and colleagues showed in a smart pharmacokinetic and pharmacodynamics meta-analysis the linear correspondence between dose level and efficacy and toxicity in more than 400 patients

treated with sunitinib under clinical trials.[23] In this sense, the results demonstrated that the highest oral exposure to sunitinib in time the greatest overall objective response rate, and longer progression free survival and overall survival with statistically significant difference. As expected, the increased exposure to sunitinib was also associated with the appearance and severity of adverse events. The proper management of adverse drug effects allows a better optimization of its efficiency and improves clinical outcomes. The incidence of fatigue was also correlated with sunitinib dose intake. However, no significant relationship was found between exposure to drug and neither severity of the fatigue nor the grade of fatigue have clearly been associated with clinical efficacy.

Molecular Mechanism for Sunitinib-Induced Asthenia

RTKs are transmembrane proteins located at the cell surface that possess extracellular ligand-binding and intracellular catalytic domains to convey environmental signals to the cell nucleus.[24] RTKs require ATP to start the phosphorylative cascade and to convey signals. Sunitinib displays a structure analogous to that of ATP, whereby it is able to competitively inhibit multiple RTKs through the blockade of their ATP-binding sites.

The exact mechanism involved in sunitinib-associated AFS remains elusive. However, sunitinib induces a decrease in blood glucose levels,[25] which interferes with the IGF-1 pathway. According to other authors, this phenomenon could be partially related to a significant quantitative and qualitative capillary regression in pancreatic islets,[26] interference with the insulin signaling pathway,[27] and alteration in glucose transport. Because sunitinib shows low target specificity and binds to the ATP-binding sites of both multiple RTKs and other unidentified proteins, it could act as a toxic agent in multiple metabolic and physiological processes. One example of an unspecific sunitinib interaction is the binding to the ATP-binding cassette (ABC) transporters ABCB1 (P-glycoprotein), ABCC1 (multidrug resistance-associated protein), and ABCG2.[28] As ABC-transporters are involved in the cellular influx and efflux of different metabolites and drugs (including sunitinib), the interaction between the ABC transporters and sunitinib could affect clinical outcomes by impairing drug delivery to cells and/or drug expulsion and detoxification.

Other examples of potential off-target interactions of sunitinib with different kinases, pathways, proteins (e.g., AMP-activated protein kinases (AMPK), HIF1 (hypoxia inducible factor 1), and facilitative sugar transporters (GLUTs)) are analyzed below.

AMP-activated protein kinase (AMPK) and sunitinib. AMP-activated protein kinase (AMPK) is a key component in different signaling pathways, acting as an energy sensor responsible for the maintenance of energy balance within the cell (Fig. 1). AMPK is activated during events entailing metabolic stress, such as nutrient starvation or intense exercise. As a result, AMPK activates a set of energy producing pathways and inhibits energy consuming pathways.[29] Thus, AMPK responds to an increase in the AMP:ATP ratio (caused by ATP depletion) and acts to balance the levels of ATP consumption and generation via anabolic and catabolic pathways.[30] This role for AMPK is particularly relevant in tissues with a very high energy demand and robust ATP consumption.

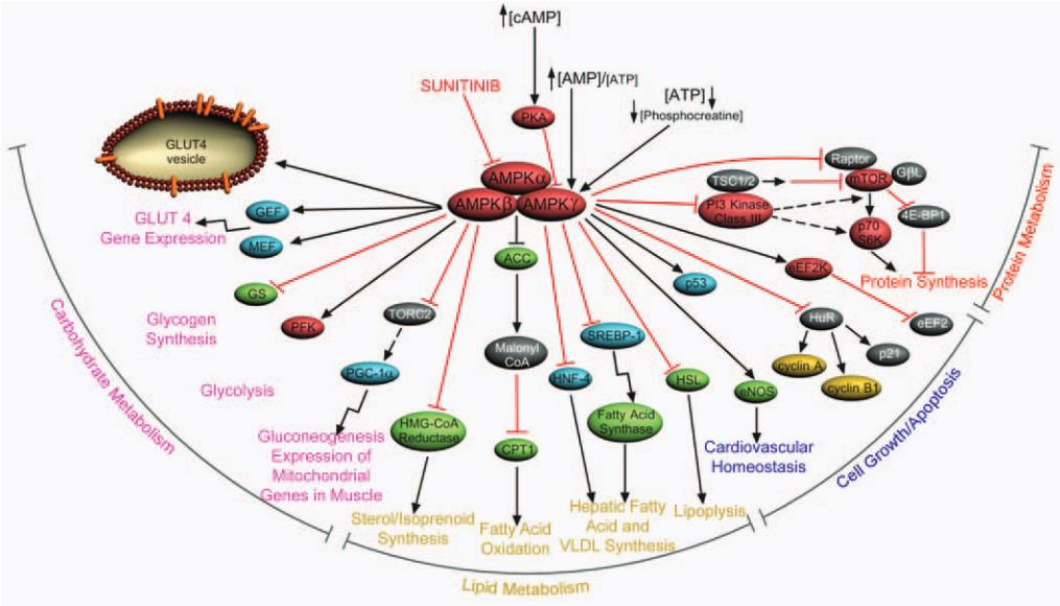

Figure 1. AMPK (AMP-activated protein kinase) is able to phosphorylate a set of targets for regulating numerous processes in response to energy depletion. These intermediary targets are in turn able to enhance (black arrows) or inhibit (red lines) different processes (such as glucose transport and metabolism, the management of fatty acids or protein synthesis).

All cells need to maintain a high ATP:ADP ratio to survive. The ATP:ADP ratio usually remains approximately constant, which is indicative of the efficiency of the mechanisms that maintain this ratio (Fig. 2).[31] In metabolic stress situations, when the cell is subjected to oxygen insufficiency and/or nutrient starvation, the ADP:ATP ratio increases due to energy deficiency. In these situations, the action of adenylate kinase (catalyzing the reaction 2ADP → ATP + AMP) maintains a minimum of ATP but also generates AMP. As a result, the AMP:ATP ratio increases, resulting in the cell's metabolic status being compromised. The increase in the intracellular AMP:ATP ratio triggers the phosphorylation and activation of AMPK, which subsequently modulates the activity of multiple downstream targets to balance ATP levels.[31] Thus, activated AMPK is able to phosphorylate and inhibit key regulatory components of signaling and anabolic pathways, including tuberous sclerosis 2 (TSC2), the mammalian target of rapamycin (mTOR), and acetyl-CoA carboxylase.[31,32] However, AMPK is phosphorylated and activated by the upstream serine-threonine kinase LKB1.[33,34] Recently, it was demonstrated that wild-type LKB1 is required to modulate the activity of AMPK and downstream targets in cells with depleted energy stores, including cancer cells.[35]

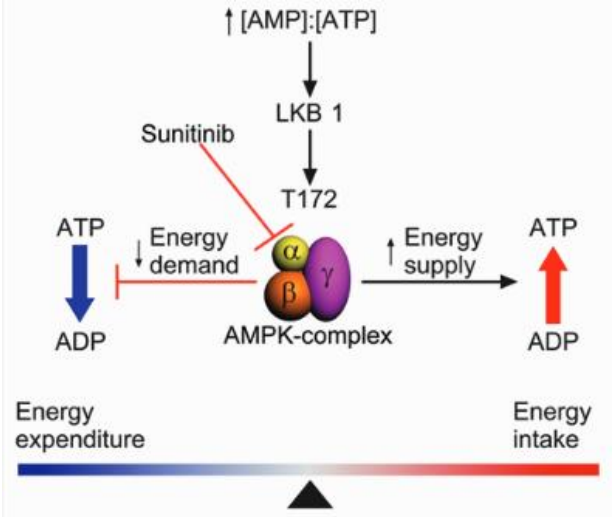

Figure 2. AMPK (AMP-activated protein kinase) is activated in response to an increase in AMP concentration and ATP depletion. The binding of AMP to the γ subunit of AMPK activates AMPK and prevents dephosphorylation of the activated phosphorylated form of the complex. Additionally, AMPK is activated by upstream protein kinases, including LKB1 and Ca^{2+}/calmodulin dependent protein kinase β. Once activated, AMPK phosphorylates a set of downstream targets, enhancing catabolic processes to obtain ATP and inhibiting anabolic processes to prevent ATP consumption.

Therefore, the inhibition, impairment or malfunction of AMPK leads to dramatic molecular alterations, which compromise the metabolic stability of the organism. Because AMPK is inhibited by sunitnib,[36-38] patients subjected to treatment with this drug are unable to control and measure their energy availability, which may contribute to their lack of energy, weakness and asthenia.

Oxygen, sugar and sunitinib. Oxygen is necessary for ATP generation because oxygen acts as the final electron acceptor in the mitochondrial electronic transport chain. Under hypoxia, cells are unable to reoxidize NADH and FADH generated during the oxidation of different carbon sources (including sugars from glycolysis) in the tricarboxylic acid cycle. Therefore, when cells are subjected to a hypoxic environment, they undergo a catabolic change. Energy/ATP generation becomes dependent almost exclusively on glycolysis. Therefore, cells activate fermentative reactions to reoxidize the NADPH generated during glycolysis and to allow this process to continue. In addition, cells under hypoxia have difficulties utilizing alternate carbon sources (such as amino acids and fatty acids) and are forced to use glucose as the primary source of energy. Because fermentative metabolism is considerably less efficient than oxidative phosphorylation in obtaining energy from glucose, hypoxic cells are forced to increase the rate of glucose uptake to fulfill energy demands. Due to their explosive and uncontrolled growth, cancer cells are frequently exposed to hypoxic conditions in tumors. Therefore, the increase in glucose uptake and the use of fermentative metabolism are hallmarks for cancer cells and tumors. The facilitative sugar transporters (GLUTs) are deregulated in various types of cancer.[39] Because this phenomenon was first described by Otto Heinrich Warburg in 1956, it is known today as the "Warburg effect."[40,41]

HIF1, a heterodimeric transcription factor composed of α and β subunits, plays a key role in the metabolic adaptation of cancer cells to hypoxia.[42] When oxygen availability is low, the α subunit is stabilized and translocated to the nucleus to dimerize with its β counterpart. Together, both subunits form the complete HIF1 transcription factor, which regulates a wide set of target genes (Table 1).[43] Among HIF targets, there are genes necessary for survival under oxygen deprivation, including those involved in glucose uptake and glycolysis.[44,45]

Table 1. HIF1 gene targets and processes where they are involved

Process	Genes
Oxygen transport	Erithropoietine (erithropoiesis)
	Transferrine (Fe transport)
	Transferrine receptor (Fe uptake)
Vascular regulation	Vascular endothelial growth factor, VEGF (angiogenesis)
	Induced Nitric Oxide Synthase, iNOS (nitric oxide production)
	Endothelin 1 (vascular tone regulation)
Anaerobic metabolism	Glucose transporter 1 (glucose uptake)
	Phosphofructokinase (glycolysis)
	Lactate dehydrogenase (glycolysis)
Cell proliferation	Insulin-like growth factor 2, IGF2
	IGF transporter proteins 1 and 3

Recently, it has been demonstrated that sunitinib is able to block the expression and activity of HIF1 in tumor cells under hypoxia,[46] and, therefore, HIF1 transcriptional targets (such as the glucose transporter GLUT1) are no longer induced. Sunitinib could indirectly impair the mechanisms by which cancer cells obtain essential carbon sources and energy (sugar uptake and glycolysis).

Our data indicate that sunitinib triggers an alteration in GLUT expression in both kidney tumor cell lines and renal cell carcinoma patients.[39] Therefore, the sequestration of energy and carbon sources from tumor cells is an additional effect of sunitinib that contributes to its anticancer efficacy. Obviously, sunitinib, as a systemic drug, can also act on normal cells and potentially induce a general deregulation of glycolysis and sugar uptake, triggering the AFS observed in treated cancer patients.

Exercise and sunitinib. In skeletal muscle, exercise triggers the stimulation of glucose transport, whether induced by insulin-independent mechanisms (based on the increase of contractile activity) or by insulin-dependent mechanisms. Thus, the cellular machinery of skeletal muscle is equipped to respond to contractile activity with a rapid increase in glucose uptake to match the high glycolytic flux. As a result, the concentration of sugar transporters in the plasma membrane is increased through the mobilization and translocation of units from the GLUT4 reservoir sequestered in intracellular pools.[47] Although the mechanism of insulin-dependent glucose uptake stimulation has already been explained,[48,49] the exact mechanism responsible for glucose uptake stimulation in response to contractile activity remains elusive. Previous reports point to intracellular calcium as the key mediator of exercise-dependent glucose uptake stimulation by the activation of different pathways, such as the protein kinase C (PKC) signaling pathway.

However, NO production and nitric oxide synthase (NOS) activity are dramatically increased in skeletal muscle subjected to intense contractile activity.[50,51] Interestingly, NO production has a deep impact on the increase of blood flow to muscle under intense activity due to its function as a vasodilator. In addition, there is evidence that NO also acts as a signaling molecule, mediating both immediate and long-term adaptive responses of muscle cells to the increase in activity.[52,53] Thus, NO stimulates muscular glucose uptake through a cGMP-mediated mechanism.[54] Conversely, the inhibition of NO production can block exercise-dependent stimulation of glucose uptake.[55] However, studies in humans subjected to exercise have produced conflicting results on the effects of NOS inhibition and NO production blockade on glucose uptake.[56] NOS activity and NO production are also linked with AMPK signaling and the increase in glucose uptake during exercise. Thus, during exercise, AMPK is activated in response to the increase in the AMP:ATP and creatine:phosphocreatine ratios,[57,58] so that it is able to phosphorylate NOS and enhance NO production.[59,60]

Therefore, since sunitinib is able to block AMPK activity,[36-38] NOS activation and the increase in NO production in response to exercise are also impaired. Therefore, NO ceases to stimulate exercise-dependent muscular glucose uptake and no longer induces vasodilation of blood vessels supplying carbon sources and oxygen to muscles.

Under normal conditions, muscle cells subjected to intense exercise experience difficulties in fulfilling their energy requirements when oxidative phosphorylation and oxygen supply are insufficient. To resolve this issue, muscle cells activate fermentative metabolism and therefore increase glucose uptake. At the molecular level, these events are triggered by the activation of AMPK and HIF1.[44,61,62] However, the muscle cells of patients treated with sunitinib are unable to respond to explosive and intense activity because the response mechanisms dependent on AMPK and HIF1 activation are blocked. In addition, in muscle cells treated with sunitinib, AMPK is unable to stop the anabolic reactions, and HIF1 is unable to activate in response to hypoxia, contributing to the increase in energy depletion and the limitation of the oxygen supply. As a result, when patients subjected to sunitinib treatment are exposed to intense and sudden activity, they display premature symptoms of exhaustion and fatigue, which result in the sensation of asthenia.

Discussion

Asthenia is the most distressing side effect observed in patients treated with TKIs, particularly sunitinib, and can severely impact the patient's quality of life. Although asthenia is part of the adverse events in common to others anti-angiogenic agents like diarrhea, skin rash, stomatitis, hand-foot skin reaction (HFSR), hypothyroidism and hematological abnormalities, there is no clear correlation with a primary VEGF signaling interference.[63]

Unfortunately, asthenia is frequently undiagnosed or ignored in cancer patients. Oncologists accept cancer-related fatigue as expected and normal, and patients are often not treated for fatigue symptoms because oncologists think there is not much they can do to manage this syndrome. It is necessary to achieve a deeper understanding of the molecular basis and mechanisms of action of antitumor agents to clinically manage adverse events. Considering different clinical observations and current metabolic and pharmacological knowledge, we propose a set of hypotheses that may explain the molecular mechanisms whereby sunitinib could elicit asthenia in cancer patients.

Adequate management of asthenia is crucial for achieving successful outcomes in patients treated with sunitinib; increased exposure to sunitinib improves clinical outcomes in terms of time to tumor progression, tumor response rate and overall survival.[64]

There is a positive relationship between exposure and incidence, but not severity, of asthenia in patients treated with sunitinib. Because asthenia is one of the most common causes of sunitinib dose reduction, there is a need to understand why this adverse event occurs and how to prevent and alleviate the issue.

Our hypothesis is based on the possible sunitinib-mediated inhibition of different metabolic and signaling pathways involved in energy balance and cell nutrition. Sunitinib inhibits the AMPK pathway, which plays a key role in maintaining the cellular energy balance. In non-malignant cells, AMPK acts during energy stress events to prevent the excessive expenditure of ATP. This effect is achieved through the specific blockade of a set of anabolic, energy-consuming pathways and the stimulation of catabolic, energy-generating pathways.[61,62,65,66] Our hypothesis is that, in cancer cells, given their high growth rate and over-consumption of ATP, AMPK is deregulated. The sunitinib-dependent blockade of AMPK[36-38] inhibits the effects of this deregulation, such as the increase in sugar uptake. On the other hand, sunitinib is able to block HIF1 activity and expression.[46] Since HIF1 enhances sugar uptake and glycolytic pathway activity,[44,62] HIF1 blockade leads to an additional level of inhibition with respect to the availability of cellular energy. Moreover, it has been demonstrated that AMPK activity is critical for HIF1 activity in cancer cells, so that the sunitinib-mediated inhibition of AMPK may act synergistically with the sunitinib-mediated inhibition of HIF1. Finally, sunitinib could act directly by blocking cellular

access to sugars (modifying the expression and/or activity of sugar transporters) or impairing metabolic processing (acting on glycolytic enzymes).

The sunitinib effects previously described could contribute to the energy deprivation of cancer cells and, therefore, to the antitumor efficacy of the drug. However, we should note that these same effects could be devastating for normal cells and could elicit diverse sunitinib-associated side effects, including AFS. The hypothetical sunitinib-dependent blockade of previously described pathways and mechanisms could decrease the cellular availability of nutrients and energy, which would lead to treatment-associated AFS. Therefore, because more specific targeted therapies are not developed, cancer patients and physicians should suffer and learn to manage, respectively, the side effects associated with current antitumor treatments.

The dose reduction may imply a decrease in drug efficacy, then it is essential in the clinical management of cancer patients to maintain the dose as higher and as longer as possible. Fatigue rarely leads to dose reductions or treatment interruptions if managed appropriately. It is critical to foresee those factors contributing to the onset and exacerbation of fatigue, including pain, anemia, depression and hypothyroidism. An understanding of the molecular mechanisms by which current antitumor drugs cause their associated side effects will contribute to the future development of better antitumor drugs.

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