Weight loss induced by tyrosine kinase inhibitors of the vascular endothelial growth factor pathway

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Weight loss, cachexia and sarcopenia are profound problems in the frail oncologic patients. With the development and increasing use of angiogenesis inhibitors in metastatic cancer patients, the question arises as to their influence on body weight and composition. Angiogenesis is not only important for the growth, development and metastatic potential of tumors but also for physiological processes in adipogenesis. A less known approach of angiogenesis inhibitors is their experimental use in obese models. This review focuses on the effects on the body weight and composition of angiogenesis inhibitors, especially of those targeting the vascular endothelial growth factor pathway. *Anti-Cancer Drugs*

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Introduction

Cancer, body weight and body composition are strongly interrelated. Weight loss occurs in 30–80% of cancer patients, with the severity depending on the type of tumor [1]. Weight loss is the result of an imbalance between energy intake and energy expenditure. Factors that contribute to a decreased intake include anorexia, nausea and vomiting, constipation, diarrhea, pain, altered taste and depression. Besides this imbalance, cancer patients are at risk of developing cachexia. Cancer cachexia is a profound metabolic process characterized by the breakdown of the muscles and abnormalities in fat and carbohydrate metabolism despite an adequate nutritional intake. This debilitating and life-threatening paraneoplastic phenomenon is present in approximately 50% of cancer patients, most markedly in patients with lung or upper gastrointestinal cancers [2]. Furthermore, cancer patients are at a risk of developing sarcopenia, a severe depletion of skeletal muscle. Sarcopenia is related to poor functional status, poor treatment response and reduced overall survival [3,4].

Weight loss in cancer patients can be a direct effect of the disease but also a side effect of most types of anticancer therapy [5–8]. However, clear insights into the prevalence and amount of weight loss directly because of the different anti cancer therapies are lacking as tumor evolution cannot be ruled out in cancer patients and the effects of chemotherapy on weight loss cannot be studied in healthy individuals because of ethical reasons. The degree of weight loss as an adverse event of anticancer therapy can be scored according to the Common Toxicity Criteria Adverse Event criteria [9]. These criteria score weight loss in grade 1–3, in which grade 1 is defined as 5–10% weight loss, without the need for an intervention, grade 2 as 10–20% weight loss or nutritional support indicated and grade 3 as weight loss of more than 20% compared with the baseline body weight, or an indication for transparenteral nutrition or tube feeding. In study reports, little attention is paid to grade 1 and 2 toxicities. But grade 1 and 2 weight loss may already be substantial and clinically relevant, especially in the frail oncologic patient. As little as 2% weight loss is already associated with shortened survival [10]. The mechanisms by which weight loss occurs during chemotherapy are not clear. Of course, anorexia, nausea, vomiting and diarrhea will contribute to weight loss during chemotherapy. Both weight loss before the start and as an adverse event of chemotherapy seem to be an indicator for poor prognosis [1]. For example, patients with advanced ovarian cancer who suffered from weight loss during chemotherapy had a poorer overall survival compared with patients who gained weight [11]. However, not all cancer patients treated with chemotherapy lose weight, and some regain weight shortly after finishing their chemotherapy. Furthermore, some therapies, especially hormonal therapies, can induce weight gain [12–14].

With the development and increasing use of angiogenesis inhibitors, the question arises as to whether these targeted drugs also have such systemic adverse events of weight loss or changes in body composition. Angiogenesis is not only important for the growth, development and ability of tumors to metastasize but also for physiological processes in adipogenesis and muscle anabolism [15]. As in all other types of cancer treatment, it is difficult to

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distinguish between the metabolic effects of cancer itself and the adverse events of angiogenesis inhibitors on body weight and composition. However, a less known, but interesting, approach of angiogenesis inhibitors is their (experimental) use in obesity. This review focuses on the effects on the body weight and composition of angiogenesis inhibitors, especially of those targeting the vascular endothelial growth factor (VEGF) pathway. In one way, this may be an unwanted side effect of anticancer therapy but in another way it may be regarded as a hypothetical innovative approach for the development of new treatment strategies of obesity.

Angiogenesis inhibitors and weight loss in cancer

Tumors are dependent on angiogenesis for growth and metastasis. They trigger the development of their own blood supply by disrupting the delicate balance of proangiogenic and antiangiogenic factors. Proangiogenic gene expression is increased by physiological stimuli, such as hypoxia. Oncogene activation or tumor suppressor gene inactivation can tip the balance in favor of proangiogenic factors. Examples of proangiogenic factors are VEGF, epidermal growth factor, insulin-like growth factor and placental growth factor. VEGF and its receptors play a pivotal role in both normal and malignant angiogenesis. Activation of the VEGF pathway leads to endothelial cell activation, proliferation and survival. Moreover, degradation of the basement membrane is necessary for endothelial cell migration and invasion, increased vascular permeability and mobilization of endothelial progenitor cells from the bone marrow into the peripheral circulation [16]. VEGF is expressed in response to hypoxia, oncogenes, or cytokines. Higher levels of VEGF (among other growth factors and cytokines) have been associated with more aggressive tumors, more accentuated weight loss and nutritional intake reductions concomitant with higher resting energy expenditure compared with control patients [17].

The VEGF pathway is considered to be the most important and best-explored pathway in angiogenesis of tumors. Multiple-treatment strategies, targeting VEGF and its receptor (VEGFR) and downstream signaling elements of this pathway, have been developed. Examples are bevacizumab, a monoclonal antibody against VEGF, used for the treatment of metastatic colorectal cancer and breast cancer, and sunitinib and sorafenib, both VEGFR tyrosine kinase inhibitors (TKIs) used predominantly in the treatment of metastatic renal cell cancer.

Less is known about the effect of VEGF TKI on body weight, as only severe weight loss is reported according to the Common Toxicity Criteria Adverse Event criteria (Table 1). Even in the case of the approved, and frequently applied, VEGFR TKIs (such as sunitinib, sorafenib and pazopanib), data on weight loss are limited. Weight loss was reported for sorafenib (inhibitor of Raf-1, B-Raf, VEGFR, platelet-derived growth factor receptor-β, fms-like TK-3 and c-KIT) compared with placebo in patients with metastatic renal cell carcinoma [18]. In this study, the sorafenib-treated patients experienced significantly more diarrhea, without significant differences in nausea and anorexia [18]. Another study that combined sorafenib with interferon alpha in patients with metastatic renal cell cancer observed all grades of weight loss in 63% of the patients [19]. In a placebo-controlled trial with sorafenib in more than 600 hepatocellular carcinoma patients, significantly more weight loss in the sorafenib treatment group was observed compared with the placebo [20]. In a phase II study of sunitinib (inhibitor of VEGFR1–3, platelet-derived growth factor receptor-α and β, fms-like TK-3, KIT, colony-stimulating factor receptor type 1 and neurotrophic factor receptor) in non-small cell lung cancer, anorexia and decreased weight were reported together (grade 1–2: 30%; grade 3: 5%) [22]. A phase I study that combined sunitinib with

Table 1 Weight loss as an adverse event of tyrosine kinase inhibitors in human studies

Reference	Type of study	Target	Finding
[18]	Sorafenib vs. placebo in mRCC patients	VEGFR, PDGFRβ, FLT-3, c-KIT	Sorafenib-induced weight loss (all grades 10 vs. 6%, grade 2; 5 vs. 3% (significantly different), grade 3–4 <1 and 0%)
[19]	Sorafenib and IFN-α in mRCC patients	VEGFR, PDGFRβ, FLT-3, c-KIT	All grades of weight loss in 63% of the patients, grade 1 weight loss in 37%, grade 2 in 23% and grade 3 in 3% of the patients
[20]	Sorafenib vs. placebo in HCC patients	VEGFR, PDGFRβ, FLT-3, c-KIT	Significantly more weight loss in sorafenib-treated patients (all grades: 9 vs. 1%, and grade 3: 2 vs. 0%, respectively)
[21]	Sorafenib in HCC patients	VEGFR, PDGFRβ, FLT-3, c-KIT	Significant loss of weight and skeletal muscle in the sorafenib-treated group during the first 6–12 months of treatment. Low BMI and sarcopenia were associated with the dose-limiting toxicity of sorafenib
[22]	Sunitinib in NSCLC patients	VEGFR1–3, PDGFRα/β, FLT-3, KIT	Anorexia and decreased weight (grade 1–2: 30%, grade 3: 5%)
[23]	Sunitinib and bevacizumab in patients with advanced solid cancer	VEGF, VEGFR1–3, PDGFRα/β, FLT-3, KIT	Grade 1–2 weight loss in 12% of the patients
[24]	Sunitinib in RCC patients	VEGFR1–3, PDGFRα/β, FLT-3, KIT	No data on weight loss reported
[25]	Sunitinib vs. IFN-α in RCC patients	VEGFR1–3, PDGFRα/β, FLT-3, KIT	No data on weight loss reported

HCC, hepatocellular carcinoma; IFN-α, interferon-α; mRCC, metastatic renal cell carcinoma; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

bevacizumab reported grade 1–2 weight loss in 12% of the participating patients [23]. Other trials using sunitinib did not report weight loss [24,25]. In conclusion, in the majority of trials, weight loss was not mentioned. In those trials that did report weight loss, the course of the weight loss after finishing the study treatment was not mentioned nor was the effect of weight loss on quality of life, treatment outcome, or prognosis.

An interesting potential new indication for the treatment with a VEGFR inhibitor (especially sorafenib) is metastatic medullary, follicular and papillary thyroid cancer. In a phase II study with patients with medullary thyroid cancer, grade 1–2 weight loss was reported in 48% of the patients treated with sorafenib [26]. Another phase II study in which patients with metastatic papillary thyroid cancer were treated with sorafenib reported grade 1–2 weight loss in 58–89% of the patients and grade 3 weight loss in 5% of the patients [27]. M.D. Anderson retrospectively reported their experience with sorafenib or sunitinib treatment in patients with dedifferentiated thyroid cancer. The results for weight loss and anorexia are presented together and were found in 20% of the patients [28]. Of further note is the fact that hypothyroidism, causing weight gain instead of weight loss, is reported as an adverse event of both sorafenib and sunitinib in up to 85% of the metastatic renal cell cancer patients, with the requirement of replacement therapy in only a minority of them [29,30].

To gain more insight into the time course of weight loss, we collected data from four phase I–II studies including approximately 70 patients who were treated with a TKI against VEGFR1–3. After 2 months of treatment, we observed a mean weight reduction of 5.1% (range, −15.8 to +5.2%), and at the end of the study, a mean weight reduction of 8.5% (range, −23.8 to +5.2%). The number of patients who experienced weight reduction of more than 5% was 45% after 2 months and 69% at the end of the study. This significant weight loss was usually already present after 2–4 weeks of treatment. The weight loss was more than clinically expected based on the limited number of patients complaining about anorexia, nausea and diarrhea complaints. Importantly, after discontinuation of the VEGFR TKIs, body weight was regained within a couple of weeks. These observations suggest that treatment with VEGFR TKIs is associated with disproportionate weight loss.

Besides weight loss, changes in body composition, apart from gastrointestinal toxicity, have been reported recently [21,31]. In a subanalysis of the Treatment Approaches in Renal Cancer Global Evaluation Trial (phase III study comparing sorafenib with placebo in patients with renal cell carcinoma), a significant loss of weight (−2.1 vs. +0.8 kg; $P < 0.01$) and skeletal muscle (−7.4 vs. −3.1 cm^2; $P = 0.02$) was reported in the sorafenib group during the first 6 months of treatment. In these first 6 months, there was no significant adipose tissue variation ($P = 0.3$) [31]. After 1 year of treatment with sorafenib, patients had lost 4.2 kg of body weight, 12.1 cm^2 of total muscle area and 33.1 cm^2 of adipose tissue area ($P < 0.01$) as assessed on computed tomography. Baseline sarcopenia was present in 52.5% of all patients, including 72% of the patients with a body mass index (BMI) of less than 25 and in 34% of those with a BMI of more than 25 kg/m^2. Women were more sarcopenic then men (65 and 48%, respectively). After 1 year of treatment with sorafenib, 71% of patients (+18.5%) met the criteria for sarcopenia [31]. Low BMI and sarcopenia were associated with the dose-limiting toxicity of sorafenib [21]. Both tumor progression and sorafenib are potentially related to progressive loss of weight and muscle; however, when correcting for tumor response on sorafenib treatment, no significant changes were found [31].

Important adverse events of angiogenesis inhibitors are anorexia, nausea, stomatitis and diarrhea. By influencing energy intake and energy expenditure, all these adverse events can cause weight loss [32]. However, most of these adverse events are less commonly reported for angiogenesis inhibitors compared with conventional chemotherapy. Moreover, edema and hypothyroidism are side effects of angiogenesis inhibitors that can contribute to weight gain. Therefore, it is hard to believe that only adverse events such as anorexia, nausea, stomatitis and diarrhea are the explanation for the pronounced weight loss observed in cancer patients treated with angiogenesis inhibitors. This suggests that angiogenesis inhibitors may have a direct effect on body weight, beyond side effects and antitumor effects.

The role of angiogenesis in adipogenesis

Healthy adults have a stable mass of adipose tissue and the supporting vasculature is quiescent [33]. Adipose tissue can grow and regress during adult life. It has been hypothesized that this non-neoplastic adipose tissue growth is dependent on neovascularization [34]. Adipose tissue is highly vascularized, with an extensive capillary network nourishing each adipocyte [35,36]. Adipose tissue is considered to be the largest endocrine gland because it produces free fatty acids, hormones, growth factors and cytokines [37]. Several of these adipose tissue-derived products influence angiogenesis, with a delicate balance between proangiogenic factors, for example, VEGF, fibroblast growth factor, insulin-like growth factor, tumor necrosis factor-α, transforming growth factor-β, epidermal growth factor, resistin and leptin and antiangiogenic factors, for example, adiponectin, endostatin, thrombospondin 1 and soluble VEGFR2 [15]. As is the case in cancer, hypoxia in adipose tissue induces high levels of hypoxia-inducible transcription factor, which increases the expression of angiogenesis-related factors including VEGF and downregulates several endogenous angiogenesis inhibitors [38–40]. A disturbance in this balance,

either pathophysiologically or because of medical interventions, can cause changes in angiogenesis.

Compared with lean mice, nutritionally induced or genetically determined *ob/ob* obese mice have significantly larger subcutaneous and gonadal fat pads, accompanied by a significantly higher blood content, increased total blood vessel volume and a high number of proliferating cells, which emphasizes the role of angiogenesis in the process of adipogenesis [41]. In several animal studies, VEGF is the most important angiogenic factor in adipogenesis and inhibition of VEGF is associated with weight loss and metabolic changes. VEGF-A is highly expressed in rat adipose tissue and its expression increases significantly during adipocyte differentiation [42–44]. In rats, the omentum was found to have the greatest VEGF secretion and the omental adipocytes were the primary source of the VEGF. Incubation of omental adipocytes under hypoxic conditions induced an increase in VEGF expression [45]. These findings suggest an important connection between adipose tissue, VEGF and hypoxia.

Effects of vascular endothelial growth factor receptor tyrosine kinase inhibitors on adipose tissue and in obesity

On the basis of this suggested connection between adipose tissue and VEGF, we reviewed the available studies on the effects of VEGFR TKIs on adipose tissue and obesity (Table 2), which are limited and only include preclinical data. In a model with murine adipocytes implanted in dorsal skin chambers, treatment with an antibody to the VEGFR-2 blocked development into adipose tissue with inhibition of both angiogenesis and subsequent vessel remodeling [46] (Table 2). After 7 days of treatment, a significantly lower vessel density compared with the control group was observed. Vatalanib (PTK787/ZK222584, a VEGFR TKI) treatment for 4 weeks in mice on a high-fat diet resulted in a significant reduction of body weight and subcutaneous and gonadal adipose tissue mass, without significant changes in blood vessel size and density [47]. Vatalanib also reduced adipose tissue development. No effect of vatalanib on blood glucose and insulin levels was found. In two earlier studies with vatalanib in nude mice on a standard diet, no decrease in body weight was observed [48,49]. A third study, using vatalanib in a murine renal cell carcinoma model, showed antitumor activity and changes in body weight [50]. In another study, a 2-week treatment with a monoclonal anti-VEGF antibody of *db/db* mice did not result in a significant difference in body weight, although the treated mice tended to gain less weight compared with the control group. At the cellular level, anti-VEGF treatment markedly inhibited the formation of smaller differentiating adipocytes and the formation of blood vessel sprouts and adipogenic/angiogenic cell clusters. In addition, the number of adipocytes was significantly reduced [51]. This effect on adipose tissue was also observed in the patients treated with sorafenib for 1 year in the Treatment Approaches in Renal Cancer Global Evaluation Trial [31].

The sarcopenia observed in patients treated with sorafenib may also be associated with the inhibition of VEGFR [31]. Inhibition of VEGFR by sorafenib in a variety of cells has been shown to result in the downstream inhibition of PI3K, AKT and mammalian target of rapamycin (mTOR). These elements are central to the activation of muscle protein synthesis by amino acids and other stimuli. The Akt/mTOR pathway is upregulated during hypertrophy and downregulated during muscle atrophy [52,53]. Phosphorylation of mTOR also results in the activation of amino acid transporters [52,53]. In this way, sorafenib treatment has a direct inhibitory effect on protein synthesis and it limits the stimulating effect of amino acids [54]. Induction of muscle anabolism by physical activity occurs through pathways involving RAF, MEK and MAPK/ERK kinases. This pathway is also inhibited by sorafenib [55]. This also illustrates that (VEGFR) TKIs target several downstream elements that are not limited to only one cancer pathway and that research should focus on the importance of these specific elements in both adipose tissue and muscle mass.

Although the observations listed above may suggest that inhibition of angiogenesis may reverse obesity, angiogenesis inhibitors have not yet been applied to treat human obesity. It is important to realize that the effects of drugs on adipose tissue are dependent on initial fat mass. A

Table 2 Effects of angiogenesis inhibitors on adipose tissue and in obesity in preclinical studies

Reference	Type of study	Target	Finding
[46]	Murine adipocytes implanted in dorsal skin chamber treatment with an antibody to the VEGFR-2	VEGFR2	Inhibition of the development of adipose tissue with inhibition of both angiogenesis and subsequent vessel remodeling
[47]	Mice treated with valatinib and a high-fat diet	VEGFR1–3	Significant reduction of body weight and of subcutaneous and gonadal adipose tissue mass, without significant changes in blood vessel size and density
[48,49]	Nude mice treated with valatinib and standard diet	VEGFR1–3	No decrease in body weight
[50]	Murine renal cell carcinoma model treated with vatalanib	VEGFR1–3	Anti-tumor activity and changes in body weight
[51]	Monoclonal anti-VEGF antibody in *db/db* mice	VEGF	No significant difference in body weight. Inhibited formation of smaller differentiating adipocytes, blood vessel sprouts and adipogenic/angiogenic cell clusters. The number of adipocytes was significantly reduced

VEGFR, vascular endothelial growth factor receptor.

drug administered to a cachetic cancer patient may have different effects on adipose tissue compared with its effects in an obese patient. Furthermore, one of the huge hurdles to overcome is the observed severe side effect of sarcopenia. A drug used to treat obesity will only be acceptable when it does not decrease muscle mass. Of importance are also other frequently occurring adverse events that impair chronic use in obese patients, such as cardiovascular disorders [56,57], during which obese people already have an elevated risk. Furthermore, drug resistance may develop [58]. Finally, knowledge of the long-term adverse events of angiogenesis inhibitors is lacking. Nevertheless, the findings suggest that further research into this area is interesting as we definitely need an answer to the still-growing problem of obesity.

Conclusion

Both in cancer and obesity, two totally distinct but major health problems, tyrosine kinase inhibition can be an important shared target for treatment.

On the basis of the limited data in the literature and our findings, we hypothesize that TKIs may be an innovative approach for the development of new treatment strategies for obesity, one of the biggest threats to human health. Although the pathophysiological connection between angiogenesis and adipogenesis is well recognized, until now, only limited research has focused on the treatment of obesity with angiogenesis inhibitors. VEGFR seems to play a central role in both angiogenesis and adipogenesis, although other targets of the described multi-TKIs cannot be excluded to also contribute to these processes.

In case of cancer, weight loss has huge consequences for the frail oncologic patient, not least on the quality of life. It is important to stress that TKIs are increasingly being applied as chronic treatments in cancer patients. Better insights into the severity, the impact and the mechanism of weight loss because of angiogenesis inhibitors in cancer patients are essential for the development of preventive measures and treatment of this side effect.

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Conflicts of interest

There are no conflicts of interest.

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