

Editorial

Endocrine Toxicities of Antineoplastic Therapy

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In recent years, the prognosis of many solid tumors has improved markedly thanks to new treatment strategies, including tyrosine kinase inhibitors (TKIs) and immunotherapy [1]. Despite their clinical relevance, these drugs are burdened with side effects, including endocrine ones, which can become serious and life-threatening if not promptly diagnosed and correctly managed [2]. TKIs act by inhibiting the catalytic activity of many kinases, consequently blocking multiple pathways linked to cell proliferation and survival, angiogenesis, and tumor invasion [3]. Thyroid dysfunctions during TKI therapies are very common, with an estimated incidence of 33.2% [4]. In patients with previous hypothyroidism, initiation of TKI therapy may require an increase in the levothyroxine dose. In patients without prior thyroid dysfunction, the most common side effect is the development of hypothyroidism possibly preceded by thyrotoxicosis due to destructive thyroiditis [5]. The pathogenesis is multifactorial and includes both direct thyroid damage, through the reduction in vascularity, inhibition of thyroid peroxidase activity, and onset of destructive thyroiditis, and peripheral effects, such as increased metabolism and clearance of thyroid hormones [5,6]. Thyroid toxicity has been proposed as a predictor of tumor response to TKIs, predicting longer progression-free survival [4,7].

The endocrine toxicity of TKIs goes beyond thyroid disorders and can also be characterized by metabolic complications, altered electrolyte and bone metabolism, and gonadal impairment. Metabolic complications are frequent when using TKIs, as dyslipidemia is reported in approximately 50% of treated patients and diabetes mellitus is reported in 15–40% of cases [8,9]. Worsening or onset of dyslipidemia has been associated with nearly all TKIs, with the exception of imatinib [10]. TKIs can reduce insulin sensitivity, inducing hyperglycemia [11]. Nilotinib appears to be the TKI with the greatest diabetogenic effect. However, it should be considered that TKIs can also cause hypoglycemia and improvement of previous diabetes mellitus [8].

Similar to TKIs, mammalian target of rapamycin (mTOR) inhibitors are also frequently associated with metabolic complications, such as dyslipidemia (both hypertriglyceridemia and hypercholesterolemia) and diabetes mellitus [12].

Both TKIs and mTOR inhibitors have been associated with electrolyte imbalances. The most common alteration is hyponatremia, due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [13]. However, other imbalances, such as magnesium and potassium losses, can also occur if EGFR (epidermal growth factor receptor) is blocked [13].

TKIs can also have an impact on bone metabolism; in fact, many TKIs have been associated with secondary hyperparathyroidism and decreased bone turnover [14]. These alterations in bone turnover could be explained by the inhibition of kinases, such as c-KIT and platelet-derived growth factor receptor A, in osteoclasts and osteoblasts [15].

Immunotherapy aims to stimulate the immune response against neoantigens on the cell surface of cancer cells [16], as tumor cells have been shown to escape immune response by exploiting the inhibitory physiological pathways of programmed cell death protein 1 (PD-1) and its ligand (PD-L1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4) [17]. These drugs have been approved for many types of cancer, but the landscape is constantly



Citation: Puliani, G.; Appetecchia, M. Endocrine Toxicities of Antineoplastic Therapy. *Cancers* **2021**, *13*, 294. <https://doi.org/10.3390/cancers13020294>

Received: 29 December 2020

Accepted: 12 January 2021

Published: 14 January 2021

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expanding with new targets and new indications [1,18]. Taking into account the ability of this class of antineoplastic drugs to enhance the immune response, it is easy to understand the high risk of immune-related adverse events associated with these treatments [19]. In particular, the dysregulation of the immune system and autoimmunity are responsible for many endocrine toxicities.

Thyroid dysfunctions are the most common side effects of immunotherapy, affecting 30% of treated patients. Hypothyroidism is more common in patients treated with PD-1 inhibitors and in combination therapies [20], and although adverse events are usually immune-mediated, it is caused by autoimmune thyroiditis in only 45% of cases [21]. PD-1 inhibitors are also associated with an increased risk of hyperthyroidism, which is usually transient and followed by hypothyroidism, although cases of Graves' disease and thyroid eye disease have also been described [21].

Contrary to thyroid changes, hypophysitis is more associated with CTLA-4 inhibitors, but again, combination therapy increases the risk [22]. Patients may have both a bulking effect, due to increased pituitary tissue, and hormonal insufficiency: isolated adrenocorticotropic hormone (ACTH) deficiency is more common in patients treated with PD-1 and PD-L1, while CTLA-4 inhibitors usually cause multiple anterior pituitary insufficiency [21]. The concomitant development of diabetes insipidus and anterior pituitary deficiency due to CTLA-4 inhibitors has been rarely described. The development of secondary hypocortisolism could be life-threatening and requires immediate diagnosis and replacement therapy [23]. More rarely, immunotherapy has been associated with primary adrenal insufficiency (0.7% of patients) [20]. While rare, it is important to consider this potential side effect, as it could present with an adrenal crisis [21]. Finally, new onset or worsening of hyperglycemia has been described in up to 2% of patients, rarely associated with diabetic ketoacidosis requiring immediate treatment [21].

1. Old Therapies, New Concerns

Although the interest in endocrine toxicities of antineoplastic therapy has grown after the diffusion of target therapies and immunotherapy, "classical" chemotherapy is not free of endocrine side effects.

The most common complication in premenopausal women is menstrual cycle interruption due to many chemotherapy regimens [24]. Moreover, the toxic effects of chemotherapy on fertility are not always reversible, and the cryopreservation of oocytes for women and of spermatozoa for men should nowadays be part of the treatment strategies of these patients [25]. Sexual dysfunction may be a long-term complication of many cancer treatments, not only in case of direct impact on the pelvic region as for gynecologic cancer or prostate cancer, but also because of the systemic effects of chemotherapy [26,27]. Moreover, in patients affected by breast or prostate cancer, hormonal therapy induces bone loss altering physiological bone turnover and exposing patients to high risk of osteoporosis and fragility fractures [28]. Chemotherapy may also cause electrolyte alterations: platinum compounds can induce sodium, potassium, and magnesium alterations, and alkylating agents and vinca alkaloids are usually associated with SIADH [13].

2. Open Issues

Despite the number of studies on the endocrine toxicity of antineoplastic therapy, many areas of uncertainty remain. First, the pathogenesis of endocrine side effects, especially for TKIs, is not always clear [8,10], and the possible association of different treatments could complicate the clinical presentation and management [29]. Second, endocrine toxicities vary between patients, suggesting that other factors such as pre-existing diseases or genetic aspects can play a role [19], and the comprehension of these confounding factors is necessary. Third, some authors have stated that the Common Terminology Criteria for Adverse Events scale is not very reliable for endocrine toxicities, since the differentiation between grades 2 and 3 is difficult, although necessary, since the clinical approaches are very different [8,30]. Finally, the increase in life expectancy of patients affected by cancer

could highlight long-term complications of these treatments, as partially described for cancer survivors.

3. Future Directions: Towards an Oncological Endocrinologist

Considering what has been reported so far, endocrine complications are a clinically significant problem for patients suffering from cancer for two main reasons: the clinical impact of endocrine toxicities, which can be life-threatening and can strongly impair quality of life, and the possible antineoplastic treatment discontinuation, frequent in the case of incorrect or late management of endocrine toxicities.

It is therefore necessary, especially in specialized oncological centers, to include the figure of the endocrinologist with a precise expertise in endocrine toxicities of antineoplastic therapy and to establish a strong collaboration between endocrinologists and oncologists in order to increase awareness on these issues and optimize oncological treatment.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

TKI	tyrosine kinase inhibitor
mTOR	mammalian targets of rapamycin
TSH	thyrotropin-stimulating hormone
SIADH	syndrome of inappropriate antidiuretic hormone secretion
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
CTLA-4	cytotoxic T-lymphocyte antigen 4
ACTH	adrenocorticotrophic hormone

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