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Annales d'Endocrinologie xxx (2017) xxx–xxx

Annales d'Endocrinologie
Annals of Endocrinology

Consensus

Introduction to expert opinion on endocrine complications of new anticancer therapies

Introduction à l'avis d'expert sur les complications endocrines de nouvelles thérapies anticancéreuses

Frederic Castinetti [a,*], Françoise Borson-Chazot [b]

[a] *Aix-Marseille University, INSERM, U1251, Marseille Medical Genetics, and Department of Endocrinology, La Conception Hospital, Assistance Publique–Hopitaux de Marseille, 13005 Marseille, France*
[b] *Fédération d'Endocrinologie, Hospices Civils de Lyon, université Claude-Bernard Lyon 1, HESPER EA 7425, 69008 Lyon, France*

Abstract

Over the last 10 years, cancer treatment has progressed, with increasing use of tyrosine kinase inhibitors, mTOR inhibitors and, most recently, immunotherapy. These molecules, however, also incur side-effects, including endocrine toxicity. As their indications are constantly increasing, due to proven efficacy, it is important for endocrinologists to know how to monitor and manage such toxicity. The French Society of Endocrinology therefore drew up a consensus statement on these points. The present introductory text summarizes the main data on these molecules' action mechanisms and the epidemiology of the main endocrine side-effects. It will be followed up by sections on organ toxicity and a summary section on patients' overall survival.

Keywords: Immunotherapy; CTLA-4; PD-1; PD-L1; Tyrosine kinase inhibitors; MTOR inhibitors

1. Introduction

Cancer is the most frequent cause of death in France. Treatment was long restricted to the triad of surgery, chemotherapy and radiation therapy, but has been changed profoundly in the last 20 years by the development of novel approaches based on understanding the underlying molecular mechanisms. Malignant tumors are characterized by autonomous cellular growth associated with proliferation/apoptosis imbalance, usually due to cell signaling pathway abnormalities. The main signaling pathway regulators are tyrosine kinases, which catalyze tyrosine residue phosphorylation in numerous molecules. Abnormal activation of certain tyrosine kinases, found in many tumors, has been implicated in oncogenesis, giving rise to the concept of tyrosine kinase inhibitors as antitumoral agents [1]. They may display anti-angiogenic action by inhibiting VEGF, FGF or PDGF-R pathways, inhibiting one or more signal transduction pathways (PI3K, MAPK, or others), or targeting a specific kinase showing abnormal activation (BRAF, EGFR, ALK, TRK, RET, etc.). Side-effects depend on targets and specificity.

More recently, the mechanisms of immune reactions to neoplastic cells have become better understood, and the means by which they can be neutralized by tumors have given rise to the concept of immunotherapy [2]. Numerous tyrosine kinase inhibitors and immunotherapy molecules are now available. In both cases, the approach differs from classical chemotherapy: firstly, the principle consists in selective targeting of the growth of a given type of tumor or in reinforcing immune system activity and, secondly, treatment is often long-course, continued until progression or relapse. Indications for targeted therapy and immunotherapy have thus increased, with promising results in many tumor sites.

DOIs of original articles: https://doi.org/10.1016/j.ando.2018.07.007, https://doi.org/10.1016/j.ando.2018.07.002, https://doi.org/10.1016/j.ando.2018.07.008, https://doi.org/10.1016/j.ando.2018.07.006, https://doi.org/10.1016/j.ando.2018.07.003, https://doi.org/10.1016/j.ando.2018.07.004, https://doi.org/10.1016/j.ando.2018.07.005
* Corresponding author.
E-mail address: Frederic.CASTINETTI@ap-hm.fr (F. Castinetti).

https://doi.org/10.1016/j.ando.2018.07.001
0003-4266/

Please cite this article in press as: Castinetti F, Borson-Chazot F. Introduction to expert opinion on endocrine complications of new anticancer therapies. Ann Endocrinol (Paris) (2017), https://doi.org/10.1016/j.ando.2018.07.001

These new molecules, however, require close monitoring, as there are many side-effects, notably including onset of endocrinopathy and metabolic disorder, the frequency of which makes teamwork between oncologists and endocrinologists indispensable. In coming years, endocrinologists will likely be dealing increasingly with patients initially seen for non-endocrine pathology but showing endocrinopathy or metabolic disorder caused by anticancer treatment. To date, however, despite general guidelines on the management of these side-effects [3], scientific societies have published no such guidelines specifically on endocrinopathy or metabolic disorder.

In 2016, the French Society of Endocrinology therefore undertook an update on the diagnosis and treatment of induced endocrinopathy. The aim was to obtain expert opinions on the management of pituitary, thyroid, adrenal and metabolic side-effects. The present introductory article describes action mechanisms and indications for the main molecules, the general mechanisms underlying induced endocrinopathy, and the methodology implemented for the consensus statement.

2. Targeted therapies

2.1. Action mechanisms and indications

2.1.1. Tyrosine kinase inhibitors

Onset of cancer is usually related to activation of one or more oncogenes, inhibition of tumor-suppressor genes or modulation of microRNA, via occasional, usually somatic, mutations, chromosome rearrangements and gene amplifications [1]. These changes alter signaling pathways and induce abnormalities in protein proliferation and/or apoptosis. Tyrosine kinases are enzymes regulating signaling pathways; they transfer an ATP phosphate group to a tyrosine residue in a protein substrate, altering its activity. They exist in the form cytosolic or coupled receptors. For example, epidermal growth factor receptor (EGFR) is a transmembrane protein with tyrosine kinase activity, showing binding domain deletion in many tumors, leading to permanent receptor activation and signaling abnormalities. Alterations in the gene coding for vascular endothelial growth factor (VEGF) or its receptor (VEGFR) lead to neoangiogenesis, favoring tumor proliferation [4].

Therapeutically, tyrosine kinases can be targeted by small molecules, or by monoclonal antibodies in the case of tyrosine kinase receptors. There are thus tyrosine kinase inhibitors that target a specific oncogenic protein (e.g., BRAF, RET, EGFR, ALK, etc.), and are effective only if that protein is activated, or signal transduction pathway inhibitors (MAPkinase and PI3kinase), and antiangiogenic molecules. A given molecule may be selective for a given tyrosine kinase or target several oncogenic proteins: e.g., vandetanib, used in medullary thyroid cancer, targets Ret, EGFR and VEGFR [1]. In all, there are some 15 tyrosine kinase inhibitors, used in indications ranging from non-small-cell lung cancer, breast cancer, gastrointestinal stromal tumor (GIST), chronic myeloid leukemia, or medullary thyroid cancer, etc.

2.1.2. Mammalian target of rapamycin inhibitors (mTOR inhibitors)

The phospho-inositide-3-kinase (PI3K) — Akt-mTor signaling pathway is involved in cell growth regulation. mTOR is a serine/threonine kinase belonging to the family associated with PI3 kinase, which is present in the form of two protein complexes: mTORC1 (5 subunits; cell growth and metabolic regulation in response to amino acids, stress, energy status, oxygen and growth factors such as IGF1 and insulin) and mTORC2 (6 subunits; cell survival regulation, cell metabolism and cytoskeleton organization in response to growth factors). Once activated, mTORC1 stimulates protein synthesis and growth, whereas the functions of mTORC2 are less well defined. mTOR inhibitors can, by inhibiting the PI3K-Akt-mTOR pathway, regulate neoplastic growth [5–8].

Therapeutically, mTOR inhibitors have been used to counter rejection, then as targeted anticancer agents. There are several indications, including pancreatic endocrine tumor, renal tumor, breast cancer, astrocytoma in tuberous sclerosis (Bourneville's disease), and certain lymphomas.

2.2. Endocrinopathies and metabolic disorders induced by targeted therapies: general data and mechanisms

These side-effects are detailed per organ in the following sections.

The endocrine side-effects of tyrosine kinase inhibitors are mainly thyroid and metabolic. Rates vary greatly according to the study, the molecule and sometimes the dose: pathophysiological mechanisms can be destructive (e.g., dysthyroidism associated with non-autoimmune thyroiditis) or functional (e.g., impairment of hormone transport or of insulin secretion, or onset of insulin resistance, although these mechanisms are hypothetical, for lack of pharmacodynamic data); generally, each molecule has its own toxicity profile.

mTOR inhibitor side-effects are frequent, and metabolic. Pathophysiological mechanisms are not well understood; it seems that a certain level of mTOR activity is necessary to prevent onset of side-effects: levels that are too low or too high may lead to side-effects and thus to endocrinopathy. Regarding carbohydrates, mTOR inhibitors reduce insulin sensitivity and secretion [9]. Regarding lipids, they lead to catabolic disorder rather than overproduction: reduced VLDL catabolism and lipase lipoprotein activity, and increased PCSK9 levels [10].

Studies of endocrinopathy following mTOR inhibitor or tyrosine kinase administration sought to determine whether it could be an efficacy marker; results so far are unclear, and no such relation can be formally asserted.

3. Immunotherapy

3.1. Immune response mechanisms and indications

"Immune checkpoint" proteins modify maladapted immune responses, and especially autoimmune responses. They are costimulation molecules necessary for immune response regulation,

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whether activation or inhibition. Cancer cells are able to modify the expression or effect of these costimulation pathways to avoid lymphocyte activation and promote tolerance. The aim of immunotherapy is to block inhibitory costimulation molecules so as to enable immune reactivation and cancer cell destruction. The main costimulation pathway activating naïve T cells is the CD28/B7 pathway, including a T-cell activating signal induced by CD28 binding to B7, followed in turn by an inhibitory signal induced by CD28/CTLA4 binding; other inhibitory signals induced by PD-1/PD-L1 binding are emitted at the inflammatory (tumor) site.

The main current treatments are based on inhibition of CTLA-4 and/or the PD-1/PD-L1 couple, enabling prolonged activation of T cells against tumoral neoantigens. Very recently, an association of both mechanisms has been used in oncology.

In practice, recognition by a naïve T cell of neoplastic cell antigenic peptides presented by antigen-presenting cells leads to an "immunological synapse" between the two cells, where T-cell surface CD28 binds to B7-1 (CD80) and B7-2 (CD86), expressed on the antigen-presenting cells, enabling final T-cell maturation and triggering an immune reaction against the neoplastic cells within the secondary lymphoid organs, with inflammatory cytokine secretion and lymphocyte proliferation. However, shortly after T-cell activation, intracellular CTLA-4 (cytotoxic T lymphocyte-associated protein 4) is sent to the membrane; CTLA-4 has a 10-fold greater binding capacity to B7 than does CD28, with which it is thus in competition [15]. CTLA4/B7 binding blocks inflammatory cytokine secretion and phase-G T cells, inhibiting the immune response and preventing overreaction [16]. CTLA-4 expression on T cells is induced by CD28/B7 binding, but is constitutive on regulatory T cells (T_{reg}) which prevents autoimmune reaction, including against tumor cells. CTLA-4/B7 binding is thus one of the main defence mechanisms in regulating autoantigen tolerance. Anti-CTLA4 antibodies block CTLA-4 binding with B7, thus promoting naïve T-cell activation and proliferation, and T_{reg} inhibition and depletion.

Activated T cells then reach the tumor bed: PD-1 (Ig superfamily) is expressed on the surface of activated T cells (and also of B lymphocytes and monocytes). PD-L1 (B7-H1) and PD-L2 (B7-DC), which are PD-1 ligands, are present on the surface of antigen-presenting cells, non-lymphoid cells such as islet of Langerhans beta-cells, endothelial cells, cardiomyocytes and cancer cells [17]. PD-1-PD-L1 binding inhibits activation and proliferation of activated T cells (bai, Gao.2017). PD-1/PD-L2 binding reduces production of proinflammatory cytokines (IL-2, IFN gamma) [18]. Anti-PD-1 and anti-PD-L1 antibodies block this pathway, enabling stimulation of an antitumoral immune response. PD-L1 can also bind to B7.1 on activated T cells (leading to specific immune side-effects) [19].

There are many principal indications for immunotherapy: melanoma, non-small-cell lung cancer, renal carcinoma, urothelial cancer, head and neck squamous cell carcinoma, stomach cancer, hepatocellular carcinoma, ovarian cancer, certain breast cancers, certain colorectal cancers, and Hodgkin's disease [20]. Results in some cancers, and particularly melanoma (which accounts for 2–3% of cancers in France) have been very promising, and it is frequently used and authorized in first line in certain indications: pembrolizumab (anti-PD-1) showed > 60% 12-month survival in aggressive melanoma [21,22], and in non-small-cell bronchial cancer with elevated PD-L1 expression [23].

3.2. Endocrinopathies and metabolic disorders induced by immunotherapy: general data and mechanisms

Immunotherapy may induce immune side-effects involving several organs. They are usually mild to moderate, but 0.5–13% of patients show grade 3–4 side-effects, requiring treatment cessation and sometimes immunosuppression treatment [24].

The exact mechanism is poorly understood [25]. In animal models, CTLA-4 inactivation leads to T-cell infiltration of tissue, autoimmune destruction and cell death. Certain human CTLA-4 polymorphisms lead to autoimmune diseases such as type-1 diabetes. CTLA-4 inactivation may thus reduce T_{reg} activity, and hence self-tolerance. Anti-CTLA-4 may also raise levels of certain pre-existing antibodies causing such immune effects [26]. Finally, there may be direct cytotoxicity against autoantigens, leading to release of new autoantigens, constituting T-cell targets, increasing the immune reaction. Why endocrine effects induced by these autoimmune mechanisms most often involve the pituitary and thyroid is not well understood: the rich vascularization of these two organs may place them more often in contact with activated T cells; direct expression of CTLA4 in the pituitary may also make it a more frequent target by direct toxicity against the organ [27,28].

3.3. Endocrinopathy as predictive factor for immunotherapy efficacy

Onset of endocrinopathy likely correlates with immunotherapy efficacy. This is especially true of hypophysitis, onset of which secondary to ipilimumab correlated with better antitumoral response in melanoma (median 19.4 versus 8.8 months survival in 17 cases in a cohort of 154 [29]); extending this study confirmed this result in a larger cohort of 228 patients, with median 21.4 versus 9.7 months survival with and without hypophysitis, respectively ($P = 0.008$) [30]. These results, like those for ITK, may involve bias due to prolonged exposure, with increasing risk of side-effects, in immunotherapy responders. In practice, onset mechanisms are poorly known; greater knowledge would shed light on the action mechanisms of immunotherapy, providing new predictive factors for response/non-response.

4. Consensus procedure: methods

Endocrinologists with expertise in managing endocrine and metabolic toxicity related to new anticancer treatments (targeted therapies, immunotherapy) met three times under the auspices of the French Society of Endocrinology between October 2017 and April 2018. Telephone conferences were also

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held during that time, to finalize recommendations. Exhaustive Pubmed literature analysis was performed for each group of organs, with the search-terms "immunotherapy", "tyrosine kinase" and "mTOR", covering the period 1990–2017.

The main target audience of the consensus statement was endocrinologists, but also oncologists and physicians prescribing new anticancer treatments. The statement was framed in terms of organ toxicity (pituitary, thyroid and adrenal) and metabolic toxicity.

Given the low levels of evidence in the literature, the consensus was formulated as expert opinions. It was then reviewed by 40 expert endocrinologists and oncologists, and presented at the French Society of Endocrinology Congress, in Nancy (France) in 2018.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

This article was reviewed and commented by Pr. Schlumberger, Pr. Girard and Dr. De la Fouchardiere, whom the authors especially thank for their criticisms and suggestions.

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