Cancer Treatment Reviews 40 (2014) 665–674

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

New Drugs

The current role of targeted therapies to induce radioiodine uptake in thyroid cancer

Eleonore Fröhlich [a,b], Richard Wahl [a,*]

[a] Internal Medicine (Dept. of Endocrinology, Metabolism, Nephrology and Clinical Chemistry), University of Tuebingen, Otfried-Muellerstrasse 10, 72076 Tuebingen, Germany
[b] Center for Medical Research, Medical University Graz, Stiftingtalstr. 24, 8010 Graz, Austria

ARTICLE INFO

Article history:
Received 23 September 2013
Received in revised form 11 January 2014
Accepted 13 January 2014

Keywords:
Differentiation therapy
Radioiodine treatment
Thyroid cancer

ABSTRACT

Targeted therapy pinpointing specific alteration in cancer cells has gained an important role in the treatment of cancer. Compounds that re-induce thyroid-specific functions could be particularly useful in differentiated thyroid cancers by rendering them susceptible to radioiodine treatment, which is relatively specific and has few adverse effects. This review describes the rationale for radioiodine treatment, considering the targets of compounds with differentiation-inducing effects, and the impact of these drugs on the expression of thyroid-specific proteins and on iodine-uptake. We survey the results from the clinical trials thus far performed. We conclude that although retinoids, thiazolidinediones, histone deacetylase inhibitors and DNA methyltransferase inhibitors do increase the expression of thyroid-specific proteins, their clinical efficacy is limited. The relatively low rate of remissions in clinical trials with re-differentiating compounds could be due to low levels of the target, heterogeneity of iodine uptake into the tumor, poor correlation of radioiodine uptake and clinical remission, and/or the slow onset of the therapeutic effect. Although the mode of action is not clear, the combination of tyrosine kinase inhibitors and RAI treatment could improve clinical responses in non-radioiodine avid metastatic thyroid carcinoma.

Introduction

Molecularly targeted therapy acts on cellular targets that participate in disease pathogenesis and is well-established for certain cancers. Effective drugs targeting signal transduction, gene expression, and angiogenesis, or inducing cancer cell apoptosis or destruction by the immune system, as well as facilitating selective delivery of cytostatic drugs to cancer cells are all already on the market. Targeted therapies have also been tested in clinical trials for the treatment of differentiated thyroid carcinoma (DTC).

Frequency and prognosis of DTC

Thyroid cancer incidence in the United States has increased in the last thirty years not only apparently because of enhanced detection but probably also as a true increase [1]. DTC is the most common type of thyroid carcinoma, mainly in the form of papillary thyroid carcinoma (PTC), accounting for 80–90% of all thyroid cancer cases. The remaining forms are follicular thyroid carcinoma (FTC) and Hürthle or oxyphilic cell carcinoma. The prognosis of DTC is generally good, with a 10-year survival rate of 85% [2]. A total of 10–20% of patients develops distant metastases [3]. In this group, the 10-year survival rate drops to 40%. Recurrence in DTC, however, occurs in up to a third of patients and only 30% of patients with distant metastases respond to radioiodine therapy with complete remission [4,5]. These patients would profit from new therapeutic options.

Role of radioiodine (RAI) treatment in DTC

First line treatment of DTC is by total or near total removal of the thyroid and if necessary lymph node dissection. According to the American Thyroid Association, radioiodine remnant ablation is indicated for patients with distant metastases, patients with lymph node metastases or with gross extrathyroidal extension regardless of tumor size, or primary tumor size >4 cm [6]. For very small papillary TC, lobectomy may be sufficient.

Both efficacy and treatment protocols for RAI treatment are disputed. Many studies reported improved prognosis and reduced disease recurrence in DTC patients after RAI treatment [7,8] but other studies question its benefit [9]. While rating of absence of visible thyroid bed uptake on whole-body scanning and of disease recurrence rate are used for evaluation of efficacy, the most important biochemical marker for evaluating progression and treatment efficacy is baseline or stimulated thyroglobulin as tumour marker in DTC. Several studies compared conventional thyroxine

* Corresponding author.
E-mail addresses: eleonore.froehlich@medunigraz.at (E. Fröhlich), richard.wahl@med.uni-tuebingen.de (R. Wahl).

0305-7372/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ctrv.2014.01.002

withholding with recombinant TSH (rhTSH) treatment and efficacy of RAI doses between 25 and 100 mCi (925 and 3700 MBq) (e.g. [10–17]. Recent trials (HiLo and ESTIMABL) showed the equivalence of low-dose RAI plus rhTSH and thyroid hormone withdrawal plus high-dose RAI, with a lower rate of adverse events in the low-dose RAI plus rhTSH group [18,19].

Independent of the applied dose, the success of RAI treatment is strongly linked to the ability of metastases to concentrate iodine. While RAI treatment improved disease-specific survival rates in patients with iodine-avid metastases [20,21], it had no beneficial effects on patients with metastases that did not take up iodine avidly [22,23].

Abnormal function of sodium iodide symporter (NIS) has been identified as most important factor for lack of RAI uptake. Although pendrin (PDS), thyroglobulin (Tg), and thyroperoxidase (TPO) expression are also decreased in PTC with BRAF mutation [24], their contribution to loss of RAI-uptake appears to be less important. Patients with positive NIS immunostaining showed a better response to RAI therapy than those without [25]. mRNA and protein levels for PDS show great inter-tumor variation; slightly reduced, dramatically reduced and absent levels of PDS have been reported [26]. TPO in TC is suppressed at both the mRNA and protein level in some studies while according to others it is not altered [27,28]. Levels of Tg mRNA varying from normal to complete loss in TC are seen [29,30]. Decreases in Tg were not related to dys-regulation of pathways common in TC [31].

Lack of NIS function is not restricted to decreased or absent expression, but can also be the result of impaired targeting, and insufficient retention of NIS at the plasma membrane. In the largest published study on tissue, overexpression in combination with intracellular localization was seen in 70% of the TC samples [32]. Intracellular NIS can cause negative feedback on NIS mRNA synthesis, and reduced thyroid stimulating hormone receptor (TSH-R) expression may also cause low NIS mRNA levels and deficient NIS migration [33].

Common genetic changes in TC, such as activation of BRAF, RAS and RET, decrease NIS mRNA. BRAF, in addition, also impairs targeting of NIS to the plasma membrane [34]. It was also suggested that NIS protein in cancer tissue is immature and has an abnormal turnover rate [32,35].

The association of mutations in BRAF and Ras genes and RET rearrangements with decreased NIS function suggests inhibition of these over-activated pathways as targets for reconstituting NIS function. Statistical data on reported frequencies of genetic mutations in PTC on the one hand and RAI uptake on the other do not support a direct link of mutations and NIS function: while 70% of PTC harbour changes in RET, Ras or BRAF genes [36], 77% of PTC show RAI concentrating metastatic lesions [3]. This situation does not support the hypothesis that modifying these altered pathways can restore NIS function. Other strategies are intended to reconstitute the expression pattern of non-transformed cells, for instance by treatment with retinoids. While some compounds for targeting over-activated pathways have already been evaluated in clinical trials, many other approaches, which will be discussed in this review, are still in the early phases of pre-clinical development.

Targeting of over-active tyrosine kinases pathways

Specific mutations and dysregulated pathways have been linked to the pathology of TC (Fig. 1). The most frequent genetic changes in DTC include BRAF, RET/PTC, and Ras genes. While mutations in all three Ras proto-oncogenes are seen in both benign and malignant thyroid tumors, other changes, such as RET and TRK are specific for TC [37]. The BRAF proto-oncogene point mutations are seen in about 30–44% of PTC and are associated with impaired

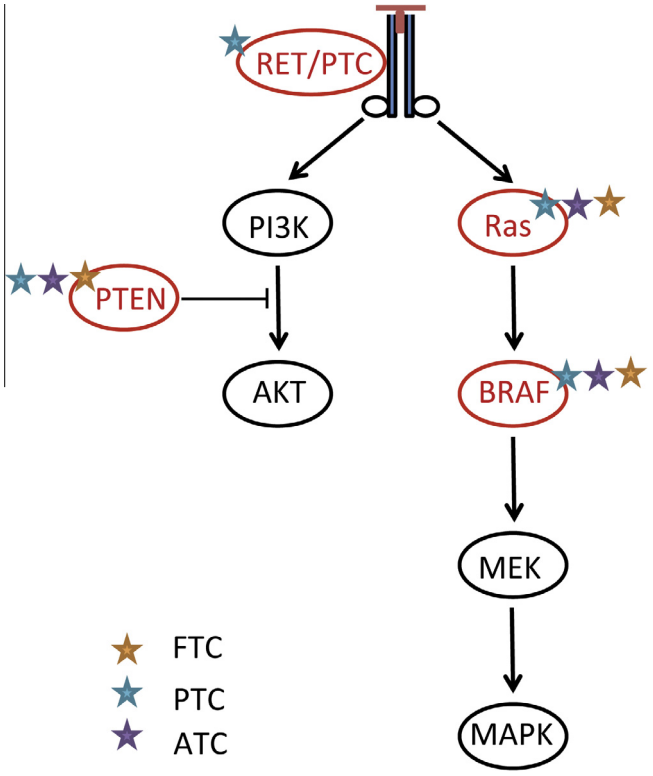

Fig. 1. Role of gene mutations leading to constitutive TK signalling in TC. Mutations have been identified mainly at the start of the TK cascade, with rearrangements of RET/PTC that activate both PI3K and Ras signalling, mutations in Ras and BRAF and of the tumor suppressor PTEN.

NIS function [34,38]. Chromosomal inversions and recombinations of the RET oncogene create chimeric RET/PTC sequences in about 30% of TC [39]. RET/PTC and TRK rearrangements and BRAF point mutation lead to constitutive signalling of MAPK kinase-ERK pathways, which communicate signals from surface receptors to the nucleus (Fig. 1). In addition, recent studies revealed that mutations in the telomerase reverse transcriptase gene are present in around 12% of all DTC and associate with an aggressive phenotype of the tumor [40]. Several other markers for aggressive growth and poor prognosis of DTC were identified by immunochemistry. Dysregulation or mis-localization of several proteins is linked to aggressive growth and poor prognosis (Table 1s, see supplemental data). Most of these are not suitable as targets, however, because they are not specific for the tumor cells, or are down-regulated in the tumors, or only their intracellular localization is altered.

Over-activated pathways are targets for tyrosine kinase (TK) inhibitors, which, in general, inhibit more than one pathway. Some of them, such as sunitinib (Sutent®), pazopanib (Votrient®), and axitinib (Inlyta®) act mainly by inhibition of VEGF signalling, while thalidomide (Contergan®) and lenalidomide (Revlimid®) act by a variety of poorly understood mechanisms independent of VEGF signalling. Many TK inhibitors, shown to have potential in preclinical models, performed less well in the clinic (for more information see one of the more recent reviews such as [41,42]). Highest partial response rates in clinical trials with sorafenib (Nexavar®) reached 21% [43], 50% for lenvatinib [44], 49% for pazopanib [45], 30% for axitinib [46], 28% for sunitinib [47], and 24% for gefitinib (Iressa®) [48]. Based on promising results in several phase II trials, a phase III trial for sorafenib in locally advanced or metastatic RAI-refractory DTC (NCT00984282) was initiated [49]. In this trial partial responses of 12% were obtained [50]. In a trial with the MEK inhibitor selumetinib in PTC, Hayes et al. reported partial responses of 3%