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Critical Reviews in Oncology/Hematology xxx (2014) xxx–xxx

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

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Targeted therapy: A new hope for thyroid carcinomas

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Accepted 21 October 2014

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http://dx.doi.org/10.1016/j.critrevonc.2014.10.012

Please cite this article in press as: Perri F, et al. Targeted therapy: A new hope for thyroid carcinomas. Crit Rev Oncol/Hematol (2014), http://dx.doi.org/10.1016/j.critrevonc.2014.10.012

Abstract

Thyroid carcinomas are rare and heterogeneous diseases representing less than 1% of all malignancies.

The majority of thyroid carcinomas are differentiated entities (papillary and follicular carcinomas) and are characterized by good prognosis and good response to surgery and radioiodine therapy. Nevertheless, about 10% of differentiated carcinomas recur and become resistant to all therapies. Anaplastic and medullary cancers are rare subtypes of thyroid cancer not suitable for radioiodine therapy.

A small percentage of differentiated and all the anaplastic and medullary thyroid carcinomas often recur after primary treatments and are no longer suitable for other therapies. In the last years, several advances have been made in the field of molecular biology and tumorigenesis mechanisms of thyroid carcinomas. Starting from these issues, the targeted therapy may be employed as a new option. The MAP-Kinase pathway has been found often dysregulated in thyroid carcinomas and several upstream signals have been recognized as responsible for this feature. RET/PTC mutations are often discovered both in papillary and in medullary carcinomas, while B-RAF mutation is typical of papillary and anaplastic histologies. Also mTOR disruptions and VEGFR pathway disruption are common features in all advanced thyroid cancers.

Some angiogenesis inhibitors and a number of RET/PTC pathway blocking agents are yet present in the clinical armamentarium. Vandetanib, cabozatinib and sorafenib have reached clinical use. A number of other biological compounds have been tested in phase II and III trials.

Understanding the biology of thyroid cancers may help us to design a well shaped targeted therapy.

Keywords: Anaplastic; Follicular; Medullary; Pathway; Papillary; Radioiodine therapy; Targeted therapy; Thyroid carcinoma

1. Background

Thyroid carcinoma accounts for 1% of all malignancies and represents a very heterogeneous disease being composed of three distinct and clinically different entities, namely differentiated (DTC), anaplastic (ATC) and medullary thyroid cancer (MTC). DTC may be further divided in papillary (PTC), follicular (FTC) and Hurtle cell carcinomas, which are characterized by a very similar clinical behavior arising from follicular cells of the gland and showing a good prognosis with a low rate of recurrences after primary therapy [1]. MTC originates from parafollicular C-cells and it cannot be treated with radioiodine therapy (RAI) being a non (t) iodium avid disease [2]. ATC is the rarest but the most lethal thyroid cancer affecting the elderly patient and being characterized by an high aggressiveness and a very poor prognosis [3].

About 90% of the DTC are effectively cured with surgery followed by RAI and suppressive endocrinotherapy, while the other 10% of patients will suffer from a recurrent disease and in one third of DTC distant metastases appear. Treatment of recurrent disease includes re-surgery, external beam radiotherapy, RAI and, rarely, chemotherapy. Recurrent MTC and ATC may be faced with the same treatment modalities except for RAI; nevertheless, the prognosis for ATC is much poorer [4].

Since re-surgery and external beam radiotherapy can rarely be administered, a RAI cumulative dose higher than 600 mCi must not be given, and the chemosensitivity of thyroid cancers is low [5], a subgroup of patients with RAI resistant disease often seeks oncologic attention and for them, few cure opportunities are at present available. For these patients new therapeutical approaches beyond chemotherapy are strongly needed.

This review will focus on the role of targeted therapies in the management of thyroid cancer patients.

2. Rationale for chemotherapy and target therapy use

2.1. Chemotherapy

Chemotherapy provides low response rates in radiorefractory thyroid cancers and the toxicity related to the employed regimens is high. Doxorubicin, either alone and in combination with platinum compounds, provides a 0–20% overall response rate (ORR). Taxanes, gemcitabine and irinotecan have been tested in the same setting of disease, showing a non encouraging activity [6,7]. In a single phase II study, paclitaxel administered as 96-h continuous infusion every 3 weeks for 1–6 cycles in 20 patients with ATC, reached a 53% of response rate (RR) [7].

A way to design an appropriate targeted therapy may be to accurately understand the molecular mechanisms involved in the tumorigenesis and neoplastic progression of thyroid cells.

2.2. Mitogen activated kinase (MAP kinase) pathway

The MAP (mitogen activated protein) kinase pathway is one of the most studied in the thyroid pathology. It has been found to be disrupted or upregulated in about 80% of (papillary carcinomas) PTC and a large percentage of ATC [8]. MAPK pathway is regulated by several upstream proteins among which RET (Rearranged during Transcription). RET is a tyrosine kinase receptor able to influence cell survival via MAPK cascade activation. A chimeric form of RET enzyme (resulted from RET-PTC gene fusion) is responsible for a gain

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