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Extended Abstract

Pharmaceutical Sciences 2018: Vandetanib in anaplastic thyroid cancer-Poupak Fallahi-University of Pisa

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Abstract

Introduction

Thyroid cancer accounts for about 1% of all cancers1 and is the most common malignant endocrinological tumor. In the last few decades, an increased TC incidence has been shown (from 10.3 per 100,000 individuals in 2000 to 21.5 per 100,000 individuals in 2012), especially for the papillary carcinoma, while mortality seems not be changed.

The increased incidence of TC was probably due to more sophisticated diagnostic procedures (ultrasonography, fine-needle aspiration, etc), but also environmental factors have been implicated (radiation exposure, pollutants, etc). Furthermore, new risk factors have emerged in last decade. Histologically, TCs include the different subtypes.

Molecular pathways in TC

In the last few decades, several molecular pathways were involved in the development of TC have been identified.

Rat sarcoma (RAS)

Rat sarcoma genes encode proteins activating MAPK and PI3K pathways.

RET (REarranged during Transfection)

RET is a proto-oncogene, which codes for a tyrosine kinase trans-membrane receptor and is expressed on tissues deriving from the neural crest including thyroid C cells but not in normal thyroid follicular cells.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) family includes VEGF A-C and placental growth factor (P1GF) and stimulates angiogenesis, endothelial cell proliferation, migration, survival, and vascular permeability binding to the VEGF receptors: VEGFR-1, VEGFR-2, and VEGFR-3.

Epidermal growth factor

Epidermal growth factor is also an important for the growth and metastasis ability of the tumour and acts by binding to EGFR, thus to stimulating VEGF expression.

Thyroid carcinoma therapy

Differentiated thyroid carcinoma

DTC was treated by surgery, followed by RAI in selected patients and levothyroxine therapy in all patients. Generally, patients with DTC have the good prognosis, with 5-year survival rate of 97.8%, when properly treated. However, 5% of patients have distant metastasis at the diagnosis or recurrent disease that cannot be treated with surgery and/or are resistant to RAI.

Medullary thyroid carcinoma

Generally, MTC is curable by surgery at early stage, followed by postoperative levothyroxine therapy. No curative systemic therapy exists for locally advanced and metastatic progressive MTC that does not respond to the conventional cytotoxic chemotherapy. TKIs are actually recommended for the selected patients with the recurrent or persistent aggressive MTC.

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Tyrosine kinase inhibitors

TKIs can act by blocking the ATP site of the tyrosine kinase receptors, and preventing the tyrosine kinase activation. Already, several TKIs are used in the treatment of various advanced cancers. Whereas TKIs do not act as selectively on pathways specific for a tumour, they have been tested on different tumours including DTC, MTC, and ATC. TKIs improve progression-free survival and stable disease rates in TC.

Vandetanib:

Vandetanib is an oral once-daily TKI that works by blocking RET, VEGFR-2, VEGFR-3, and EGFR and to a lesser extent VEGFR-1.The most important antitumoral effect of vandetanib, in vivo, is an "indirect" effect on angiogenesis, interfering with the EGFR-induced production of angiogenic growth factors. Several clinical trials have been conducted to evaluate the efficacy & tolerability of vandetanib in patients with TC.

- Phase I trials
- Phase II trials

Recently, Phase I/II trial has been conducted for the adolescents and children with metastatic or locally advanced MTC. In this trial, 16 patients were treated with vandetanib 100 mg/m2 /day, concluding this dosage is a well-tolerated and highly active treatment for the adolescents and children with locally advanced or metastatic MTC, MEN2B.

- Phase III trials

A randomized, double-blind, placebo-controlled multicenter Phase III trial (ZETA trial) was conducted in 331 advanced (5% of all patients) or metastatic (95%) MTC patients.

Safety and tolerability

Clinical studie's were showed that vandetanib treatment is associated with several AEs but it has an acceptable tolerability because AEs are generally mild and manageable. The most frequent AEs in vandetanib-treated patients are diarrhoea, rash and folliculitis, nausea, QTc prolongation, hypertension and fatigue, headache, decreased appetite, and acne.

Combination studies

Several studies have been evaluated the effectiveness of the synergic action of different antineoplastic drugs in combination studies. It has been shown that the combined therapy with bortezomib & EGFR inhibitors (gefitinib, vandetanib, and cetuximab) induced a synergic inhibition of neoplastic growth. Here currently, nonrandomized, Phase I/II trial of the combination of vandetanib plus bortezomib is recruiting patient's with solid tumours.

Other studies have been evaluated the combination of vandetanib and irinotecan. Preclinical data showed that vandetanib has ant proliferative antitumor activity *invitro*, which acts' in a sequence-dependent manner with chemotherapeutic agents, such as irinotecan, in colon cancer cell lines. A subsequent study was conducted in a murine xenograft model of human colon cancer treated with vandetanib in combination with irinotecan that showed an additive synergic effect of these drugs. Another study will evaluated the response to vandetanib, radiotherapy, & irinotecan of human LoVo colorectal tumoral cells, demonstrating that vandetanib significantly increases the antineoplastic effects of irinotecan and radiation when given in combination, resulting in a reduction of tumour growth.

Conclusion:

Vandetanib is emerging as potentially effective option in the treatment of advanced MTC. Furthermore, vandetanib seems to be promising therapeutic option in patients with the advanced dedifferentiated PTC that is not responsive to traditional therapies or RAI. The most important effect of vandetanib in aggressive MTC is a prolongation of PFS and a stabilization of the disease, while overall survival is not changed. Significant side effects have been observed with vandetanib therapy and severe side effects can require the suspension of the drug. Several studies are currently working under way to evaluate the long-term efficacy and tolerability of vandetanib in MTC, and in dedifferentiated PTC, because progression can be slow. The efficacy of vandetanib in patients with MTC in long-term treatments could be overcome the resistance to drug that could arise from the activation of alternate mitogenic signals.

The effectiveness of the treatment could be ameliorated by the possibility to test sensitivity of primary TC cells from each subject to different TKIs. Further research is needed to determine the ideal targeted therapy, based on molecular characterization of tumour and of the host factors, to obtain the best response in terms of survival and quality of life.

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