Towards effective treatment for papillary and follicular metastatic thyroid cancer

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Introduction

More than 80% of patients with papillary and follicular thyroid carcinoma have no evidence of disease following initial treatment with surgery and radioiodine (^{131}I). At least two thirds of patients with recurrent neck disease and one third of those with distant metastases will achieve a complete remission with current therapeutic modalities. However, there is still a small percentage (between 2 and 5%) of patients with progressive disease for whom new therapeutic modalities are needed [1,2].

Standard treatment for recurrent or persistent disease Radioiodine alone can effectively treat tumour foci exhibiting ^{131}I uptake as long as a radiation dose of at least 8000 cGy can be delivered, whereas response is virtually non existent for doses below 3500 cGy. Thus, thyroid-stimulating hormone (TSH) stimulation, low iodine diet and administration of large activities of radioiodine are mandatory.

Response to ^{131}I in lymph nodes and distant metastases is better when lesions are small (<1 cm in diameter). In patients with large tumour deposits, ^{131}I treatment may induce a partial response, but rarely leads to cure. Surgery for lymph nodes or bone metastases, and external radiation therapy for bone metastases may thus be warranted. Embolisation, radiofrequency or cement injection may delay tumour progression and produce relief of symptoms.

Thyroxine treatment at suppressive doses will obviate the stimulation of tumour growth induced by TSH. However, tumour may continue to grow suggesting other defects in tumour growth control.

Cytotoxic chemotherapy

Of the drugs administered to patients with metastatic differentiated thyroid carcinomas, the only widely tested agent was doxorubicin. Response rates ranged from 0% to 22% with all responses being partial and only of a few months duration, without any benefit for survival. Combination of doxorubicin with cisplatin yielded similar response rates to doxorubicin alone, but with the added drawback of major toxicity. When given when TSH was raised, this combination induced few tumour responses. Combination of doxorubicin with radioiodine in patients with uptake in metastases did not improve the response rate.

Very few trials have been reported with other cytotoxic agents, and they concerned limited series of patients; mitoxantrone and etoposide appeared to be ineffective; paclitaxel produced anecdotal responses with uncertain durability.

Chemotherapy should therefore be given only to the few patients with progressive metastatic disease refractory to radioiodine treatment in the context of prospective controlled trials with new antineoplastic agents. Even in these patients, the indication for chemotherapy should always be weighed against long survivals without systemic treatment when tumour burden is limited. High FDG uptake on PET scan can depict more rapidly progressing lesions that may require local or systemic treatment.

Biotherapies: past-experience

Non specific agents

Treatment with interferon-α or interleukin-2 induces lymphocytic thyroiditis in a significant proportion of patients treated for non-thyroid disease. In thyroid cancer patients, either alone or in combination with doxorubicin, they failed to yield any tumour response. Such was also the case with somatostatin analogs.

Trials aimed at restoring radioiodine uptake

Retinoic acid analogs in some *in vitro* studies decrease the tumour growth rate and increase the expression of the sodium-iodine symporter (NIS). In clinical trials,

retinoic acid analogs produced the reappearance of ^{131}I uptake in few patients, but no clinical benefits were obtained with subsequent ^{131}I treatment. Also, they did not produce significant direct effects on tumour growth. Because the decrease or loss of NIS expression in tumour cells has been related to DNA hypermethylation of its promoter region, the use of an inhibitor of DNA methylation (decitabine) is currently tested in thyroid cancers that no longer effectively concentrate iodine. Another trial uses SAHA, an orally available histone deacetylase inhibitor.

Gene therapy with NIS may induce iodine uptake *in vitro* in infected tumour cells and *in vivo* in xenografted tumours by direct injection into the tumour. However, the tumour retention of radioiodine is short and the resulting radiation dose is low.

The future: molecular targeted therapies [3–5]

In thyroid cancer cells, the MAP kinase pathway plays an important role, along with overexpression of tyrosine kinase receptors [3], including fibroblast growth factor (FGF), epidermal growth factor (EGF), hepatocyte growth factor (c-Met), vascular endothelial growth factor (VEGF), insulin and insulin-growth factor 1 (IGF1) receptors.

Mutations in genes encoding signalling molecules of the MAP kinase pathway has been found in 80% of papillary thyroid carcinomas, and are believed to be the initiating event [4]. These mutations include *RET/PTC* rearrangements, and activating point mutations of the *RAS* and *BRAF* genes. In adult sporadic papillary thyroid carcinoma, *RET/PTC* rearrangements are found in 5–30%, *RAS* mutations in about 10% and *BRAF* mutations in about 40% of cases, with no overlap between these mutations. *BRAF* mutations are found in the classical and in the poorly papillary histotypes. In papillary carcinomas occurring after radiation exposure during childhood, *RET/PTC* rearrangements are more frequently observed and *BRAF* mutations are less frequent.

In follicular carcinomas, *RAS* mutations are found in 30–40% of cases, and *PPARγ–PAX8* rearrangements in about 40% of cases; *RET/PTC* rearrangements and *BRAF* mutations have not been found. These data suggest that different pathways may lead to either papillary or to follicular thyroid carcinomas. Of note, P53 mutations are virtually non-existent in papillary and follicular differentiated thyroid carcinomas.

Also, the activation of the phosphatidylinositol 3-kinase (PI3 kinase) pathway may play a role in the pathogenesis of thyroid cancers. Most tyrosine kinase receptors can signal through the PI3K pathway.

Interferences with these signal transduction pathways

ZD6474 and AMG706 are oral inhibitors of VEGR, EGFR and RET kinases. Their clinical activity in thyroid cancer patients is planned to be tested in phase II trials.

No data is available on thyroid cancer with farnesyltransferase inhibitors (FTI) that prevent translocation of activated Ras protein to the cytoplasmic membrane (this tanslocation is necessary for signal transduction).

A potent and selective small-molecule inhibitor of Raf-kinase, BAY 43-9006, is being tested in thyroid cancer in a phase II trial.

The mamalian target of rapamycin (mTOR), plays a critical role in the transduction of proliferative signals mediated through the PI3K-Akt signal transduction pathway. Inhibition of mTOR can be achieved by rapamycin as well as its analogs, and this is being tested in a phase I trial.

Hsp 90, the 90-kDa heat shock protein is a chaperone molecule involved in the protein activation and stabilisation of Raf-1 and Akt. Blockade of Hsp 90 by geldanamycin and its related compound, 17-N-allylamino-17-demethoxy-geldanamycin (17-AAG) results in enhanced degradation of these signalling molecules. *In vitro*, this leads to growth arrest and to apoptosis. Phase I/II studies are currently recruiting patients for treatment with 17-AAG.

Other inhibitory mechanisms

Anti-EGFR antibodies and small molecules targeting the kinase activity of the EGFR have been tested with success in thyroid cancer cell lines, but thyroid cancer patients have not been treated with this agent.

No specific data on thyroid cancer patients are available with the recombinant antibodies directed against VEGF or VEGF receptors, or with small molecules targeting the tyrosine kinase of the VEGFR. The use of antiangiogenic agents may enhance the therapeutic efficiency of external radiation or radioiodine therapy.

Several phase I/II/III trials are currently open with pro-apoptotic agents, with celecoxib (a COX-2 inhibitor), with bortezomib (a proteasome inhibitor), or with depsipeptide (a matrix metalloproteinases inhibitor).

Conclusions

Papillary and follicular carcinomas represent a fascinating model. A large majority of patients can be cured, some may survive for decades despite persistent disease. Finally, only few patients with progressive

disease may require novel therapeutic modalities. In most patients, the initiating event may be found and represent a strong rationale for the use of molecular targeted therapy.

References

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