TYROSINE KINASE INHIBITORS IN ADVANCED THYROID CANCER

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Abstract. In the last decades significant progresses have been made in the field of cancer therapy, among all the so-called "targeted therapy". Tyrosine kinase inhibitors (TKIs) are example of these new strategy and they have been used in many solid and hematologic tumors. TKIs are small molecules that inhibit tyrosine kinases, enzymes responsible for the activation of signal transduction cascades, through phosphorylation of various proteins. TKIs have been used in advanced thyroid cancer refractory to conventional treatment.
So far, in MTC patients TKIs (motesanib, sunitinib, vandetanib, sorafenib, cabozantinib, axitinib) have determined an overall objective response (stable disease and partial response) ranging 45-92% while in DTC patients between 49-82%.
From 2005 to 2010 we participated in 5 international randomized trials, double-blind or in a single arm, using 5 different TKIs. We enrolled 21 patients with MTC patients and 10 with DTC. Among patients with MTC, taking the drug and not the placebo, we observed 38% of stable disease and 22% of partial response. In DTC patients we had nearly 50% of objective response.
In general, limitations using TKIs are represented by adverse reactions, principally dermatological, and resistance.
In conclusion, TKIs seem to be a promising class of drugs to treat advanced thyroid cancer, refractory to conventional treatment with quite manageable side effects.

Keywords: thyroid cancer, tyrosine kinase inhibitor, targeted therapy

Thyroid cancer is represented by differentiated thyroid carcinoma (DTC) constituted by papillary and follicular histotype, medullary thyroid cancer (MTC, arising from the parafollicular C-cells) and anaplastic thyroid cancer (ATC).
Most patients with differentiated thyroid cancers have limited disease and display an excellent prognosis with standard treatment, consisting of surgical resection, radioactive iodine (131I) and l-tyroxine suppressive therapy. Distant metastases at the time of diagnosis are very rare (5% of the patients) and recurrent disease occurs in another 10-15% of the cases. About half of these cases can be cured with conventional radioiodine therapy or additional surgical procedures, but another half of these tumors became poorly differentiated, lose the ability to take up radioiodine and have a poor survival (15% at 10 years) [1-3]. No survival benefit has been demonstrated with chemotherapy with cytotoxic drugs (doxorubicin alone or in combination with other drugs) or external beam radiotherapy.
Regarding MTC recurrent disease develops in approximately 50% of the cases and distant metastases are present, at first diagnosis, in 7-23% of the MTC patients. For metastatic MTC the overall survival rate is only 25% at 5 years and surgery is the only treatment option since radioactive iodine and TSH suppressive therapy have no role [4]. Also in MTC chemotherapy is not effective.
ATC represents less than 5% of all thyroid cancer but is one of the most aggressive human tumors and its prognosis is very poor, survival rate rarely exceeding 6-12 months. It can arise de novo or from pre-existing DTC. Therapy is based on surgery, whenever it is possible, external beam radiotherapy and chemotherapy but with palliative effects.
So, more effective therapy clearly needed for differentiated thyroid cancer resistant to radioactive-iodine, metastatic MTC and in all cases of anaplastic thyroid cancer. Conventional external-beam radiation and chemotherapy offer only marginal benefit for these cancers. So, new treatment are required and, based on knowledge of the molecular pathways involved in thyoid cancerogenesis, a new approach is costituted by the so called "targeted therapy".
Evidence has been accumulated in experimental models and clinical trials that, among several aberrant molecular mechanisms, one specifice oncogene or a particular pathway may be sufficient to maintain the malignant phenotype. This concept has been defined as "oncogene addiction" [5]. The reversal of this abnormality can lead to inhibition of cancer growth and/or apoptosis and it is the rationale for the targeted therapy. An

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example of this phenomenon is the inactivation of angiogenetic genes leadind to inhibition of tumor invasion, angiogenesis and recurrence.

An example of targeted therapy is constituted by tyrosine kinase inhibitors (TKIs), small molecules that inhibit tyrosine kinases, enzymes responsible for the activation of signal transduction cascades, through phosphorylation of various proteins. Many TKIs do not have a single target but may inhibit several proteins potentially involved in tumor growth.

A turning point in the field of TKIs started with the development of imatinib. This drug was the first kinase inhibitor approved by the FDA for the treatment of chronic myeloid leukaemia. Imatinib therapy resulted in a significant improvement of tumor response, overall survival and patients' outcome in CML compared to previous therapeutic regimens.

In recent years, other new molecules have been developed acting directly on neoangiogenesis and/or cancer cells proliferation. Some of these molecules have been used in progressive advanced thyroid cancer with promising results. The clinical response to these drugs is always assessed by radiological evaluation using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

So far, in MTC patients TKIs (motesanib, sunitinib, vandetanib, sorafenib, cabozantinib, axitinib) have determined an overall objective response (stable disease and partial response) ranging 45-92% while in DTC patients between 49-82% [6].

From 2005 to 2010 we participated in 5 international randomized trials, double-blind or in a single arm, using 5 different TKIs. We enrolled 21 patients with MTC patients and 10 with DTC. Among patients with MTC, taking the drug and not the placebo, we observed 38% of stable disease and 22% of partial response. In DTC patients we had nearly 50% of objective response. Moreover, in an ongoing off-label trial using sorafenib we have tested the drug in 20 advanced thyroid cancers: among them we observed a stable in disease in 7 patients and a partial response in 1 patient.

In general, limitations using TKIs are represented by adverse reactions and resistance.

Regarding side effects, TKIs are generally quite well tolerated with much less toxicity than chemotherapy. The most common adverse events are represented by constitutional symptoms such fatigue, weight loss, diarrhea and nausea, although only rarely they reach moderate-severe grade, for which temporary discontinuation or dosage reduction is required.

Hypertension is a common effect to all VEGF inhibitors; total incidence varies from 17 to 56% with grade ≥3 varies between 2-25%. Recently, a consensus regarding the initial assessment and consequent management of patients developing hypertension while receiving VEGF pathway inhibitors has been reported [7].

Common to almost all TKIs is the occurrence of a series of cutaneous adverse events including hand-foot skin reaction (HFSR), mucositis, papulopustolar rash, alopecia and xerosis. Usually, these events occur within 6 weeks of therapy and often in the first 2 weeks. So far, no consensus exists about the treatment algorithm to follow in these cases, but expert recommendations and proposed algorithm have been delivered [8].

Another common side effect with some TKIs is the increase of serum TSH that often requires an adjustment of L-tyroxine therapy. The intimate mechanism of this alteration is still unknown but an interference in thyroid hormone metabolism or a decrease in l-tyroxine absorption have been postulated.

An issue of all TKIs is represented by resistance phenomenon that may be intrinsically or developing during therapy and it implies a tumor cells insensitivity to the drugs.

Another issues is that these drugs have a cytostatic effect so they have to administrated chronically and they don't cause tumor cell apoptosis; an alternative approach could be the association with cytotoxic drugs as it has now be using in other ongoing clinical trials.

In conclusion, TKIs seem to be a promising class of drugs to treat advanced thyroid cancer, refractory to conventional treatment with quite manageable side effects.

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