**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
example of this phenomenon is the inactivation of angiogenic genes leadind to inhibition of tumor invasio-
An example of targeted therapy is constituted by tyrosi-
sine kinase inhibitors (TKIs), small molecules that inhibit tyrosine kinases, enzymes responsible for the acti-
vation of signal transduction cascades, through phosphorylation of various proteins. Many TKIs do not
have a single target but may inhibit several proteins poten-
tially involved in tumor growth.
A turning point in the field of TKIs started with the de-
velopment of imatinib. This drug was the first kinase in-
hibitor 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 de-
veloped 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 (RE-
CIST) criteria.
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termined an overall objective response (stable disease and partial response) ranging 45-92% while in DTC pa-
tients between 49-82% [6].
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alized 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 pa-
tients 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, di-
arrhea and nausea, although only rarely they reach
moderate-severe grade, for which temporary discon tin-
uation 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, papulopustular rash, alope-
cia 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 in-
crease 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 thy-
roid hormone metabolism or a decrease in l-tyroxine
absorption have been postulated.
An issue of all TKIs is represented by resistance phe-
nomenon that may be intrinsically or developing dur-
ing therapy and it implies a tumor cells insensitivity to
the drugs.
Another issue is that these drugs have a cytostatic ef-
fect so they have to administered chronically and they
don’t cause tumor cell apoptosis; an alternative ap-
proach 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 con-
tventional treatment with quite manageable side effects.

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