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Treatment with Kinase Inhibitors Plus Myo-Inositol as Re-Differantiating Agents in Iodine Refractory Cancers

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Abstract

Background and aim: Recently pre-clinical studies have confirmed that the inhibition of the MAP kinase pathway can induce re-differentiation of radioiodine refractory(RAIR) follicular-cell thyroid cancers (TC). The aim of this trial is to investigate whether the combination of kinase inhibitors (KIs) with myoinositol (MI) can induce or potentiate the re-uptake of RAI in cancer cells. Overview and methods: This is an open label, non-pharmacological, multicenter, randomized pilot study. Patients will be divided into 2 groups: a) a control group in which patients are treated with KIs (T plus D or L); b) a group, in which patients are treated with the same KI and in addition with MI. After 30 days of MI treatment, all patient, treated with L-T4 at a semi-suppressive dosage as per clinical practice, will be stimulated with recombinant human TSH (rhTSH) (days 31 and 32). Then at day 35 patients will be submitted to whole-body scintigraphy, with hybrid imaging where possible (SPECT/TC), after administration of the diagnostic activity (185-222 MBq) of 123-I in accordance with the SNMMI/EANM guidelines. Blood samples will be collected before starting MI therapy (day 0), after 30 days of MI therapy and then at days 31, 32, 33, 34 and 35 after MI therapy. QoL will be assessed at beginning of the MI treatment and at the end of its administration. The primary endpoint is to evaluate the restoration of the 123 uptake in RAIR follicular cell-derived TC patients already on KIs therapy alone and on KIs therapy plus MI. Restoration of the 123 uptake will be evaluated in target lesions. Conclusions: The study evaluates the possible re-differentiation of RAIR cell-derived TC in patients treated with KIs plus MI. The re-uptake of iodine will be evaluated as the primary end point, and Tg values and QoL will be evaluated as the secondary end points. The main limitation of the study is that we do not investigate any clinical effects. We will have to post-pone the clinical analysis to a later date after the administration of RAI for therapeutic purposes.

Keywords: thyroid cancers; MI; KIs; QoL

1. Introduction

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Follicular cell-derived thyroid cancer (TC), with the exceptions of poorly differentiated TC and anaplastic TC, conserves some sodium iodide symporter (NIS) expression in the basal plasma cell membrane. The NIS amasses iodine in the thyroid cell by transporting two sodium ions and one iodine ion into the cytosol, and iodine is then incorporated and stored in thyroglobulin, which is referred to as organification. Radioiodine (RAI) thus represents one of the first theragnostic agents in medicine. RAI is the cornerstone of treatment, after total thyroidectomy (TT), for adjuvant purposes in intermediate and high-risk differentiated follicular cell-derived TC. RAI is also the main therapeutic option in the metastatic disease, which occurs in less than 10% of cases but represents the most frequent cause of TC-related death. However, unfortunately a percentage of these metastatic cancers can become RAI-refractory (RAIR), and although rare, metastasis can be RAIR even from the initial diagnosis (2–5). Although there is no universal definition of RAIR, RAIR refractory TC have been classified into four categories as shown in Table 1 (1).

For RAIR thyroid cancers (RAIRTC), the choice of possible therapeutic strategies completely changes. Whenever possible, local therapy, above all surgery, may be possible but in the case of diffuse significant progression of widespread metastatic disease, only systemic therapy offers some chance of treatment. For a long time a systemic effective therapy for RAIRTC was an unmet need,, however in the last few years protein kinase inhibitors (KIs) have led to a turning point for the treatment of these tumors (6,7).

Protein kinases catalyze the transfer of the phosphate group from a nucleoside triphosphate donor to target proteins, resulting in a conformational change in the protein, which alters its function. Protein kinases are frequently involved in signal transduction (membrane signals, i.e. receptors) or in post-receptor cascade activation with the regulation of growth, cell cycle, apoptosis and differentiation. Notably, among all these complex intracellular signal transduction pathways mediated by protein kinases, the MAPK and PI3K-Akt pathways are well known to be implicated in thyroid tumorigenesis. KIs are small molecules which, with different mechanisms, can interfere with the active phosphorylating domain of protein kinases, thus blocking the enzymatic function and entire post-receptor cascade.

Several studies have demonstrated that MAPK pathway activation is associated with dedifferentiation and in particular NIS repression. The Cancer Genome Atlas (TCGA) Research Network highlighted that BRAFV600E-mutated PTC (which had the strongest activation of the MAPK pathway) showed the most dedifferentiated state, i.e., low expression of some thyroid differentiation genes such as the gene encoding for the NIS (*SCLC5A5*), thyroglobulin (Tg) or thyroid peroxidase (TPO). The anti -proliferative effects of KIs may thus re-induce the ability to uptake iodine and the possible role of re-differentiation is currently under investigation in several trials.

Several *in vitro* studies have demonstrated an increase in NIS expression and/or iodine uptake (IU) in human thyroid cancer-derived cell lines with different MAPK pathway KIs. These were specifically selective KI inhibitors (sKIs), namely BRAFV600E KI, such as vemurafenib (V) (8,9) or dabrafenib (D) (10) and MEK inhibitors such as selumetinib (10,11) as multi KIs (mKIs) such as cabozantinib (C) (12) or sorafenib (11,12).

The first clinical phase II study to test the mKI sorafenib (S) reported that of the 20 patients evaluated for re-differentiation, only one showed a weak restored uptake of RAI in an occipital skeletal metastasis on a diagnostic whole-body scan (WBS), but which was not confirmed on the therapeutic WBS (13). Renewed interest in the re-differentiation strategy arose after a study by the James Fagin laboratory (Memorial Sloan-Kettering Cancer Center) (14). In this latter study, an ingenious mouse model expressed the BRAFV600E oncogene in the thyrocytes with the ability to switch the expression of BRAFV600E on and off with the administration or withdrawal of doxycycline. The pharmacological inhibitors of MEK (selumetinib) or the BRAFV600E inhibitor (dabrafenib) showed partially restored thyroid-specific gene expression and radioiodine uptake. Following this preclinical *in vivo* model, a pioneer study by the Memorial Sloan-Kettering Cancer Center by Ho et al. in 24 patients with PTC or FTC or PDTC confirmed the ability of selumetinib to

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restore radioiodine uptake in 44% of the BRAFV600E-mutated DTC patients who were then treated with I-131, resulting in partial tumor responses in 11% of these patients (15).

More recently a considerable number of pre-clinical studies have confirmed that the inhibition of the MAP kinase pathway can induce re-differentiation and tumor response in BRAFV600E-mutated cancer with clinical benefits (16–20).

Most studies in vitro and in vivo are with sKIs, however some studies have also shown that Cabozantinib (C) and Lenvatinib (L) increased iodine uptake (12,21,22). This is not surprising considering that although mKIs have multiple targets, and although the main effect of L is on VEGFR 1-3, this drug also interacts with PDGFR and PI3K/AKT pathway.

Overall, these data point to the possible role of myo-inositol (MI) to potentiate the action of KIs.

MI is a carbocyclic polyol and belongs to the inositol (IS) family which consists of nine possible structural isomers. MI is the most widely IS distributed in nature, and is present in fresh fruits, vegetables, cereals, legumes, and nuts. However, MI is also endogenously synthesized from glucose-6-phosphate, and in some tissues, presents approximately 99% of intracellular IS. MI is a fundamental component of structural lipids in cell membranes such as phosphatidylinositol (PI) and different phosphatidylinositol phosphates (PIPs) which are precursors for many other IS-containing compounds involved in signal transduction, vesicle trafficking, cell differentiation and growth.

The generation of MI and its intracellular derivates are under the control of TSH. At slightly higher physiological concentrations, TSH activates the phospholipase C (PLC)-dependent inositol phosphate Ca_2^+/diacylglycerol (DAG) pathway, with the formation mainly of inositol 1,4,5-triphosphate (IP3). IP3 increases the concentration of intracellular Ca_2^+ by favoring its release from the endoplasmic reticulum. Calcium is essential for DUOX2 activation and H202 generation, and activates the entire complex DUOX2/TPO and thyroid hormone synthesis. Other IS polyphosphates (3.4 and 3.4.5 polyphosphates) can inactivate AKT, which is a serine/threonine-specific *protein* kinase also known as protein kinase B. Because activating mutations in proteins of the PI3K/Akt/mTOR pathways are implicated in tumorigenesis and the dedifferentiation of thyroid cells, the above mentioned IS polyphosphates may exert a protective (anti-tumoral) role. Another potential effect of the IS family is the positive role of PIP5K in the recruitment and activation of EZRIN which binds NIS and increases its membrane residency.

In summary, MI may increase the uptake and retention of iodine inside the tumor cell and exert a block on the dedifferentiation pathway and the synergistic effect of MI together with KI is supported by strong evidence. The aim of this trial is thus to investigate whether the combination of MI with sKI and mKI can induce or potentiate the re-uptake of radioiodine in cancer cells. Moreover our protocol regarding the use of KIs as re-differentiating agents differs significantly from most of other protocols.

2. Materials and Methods

2.1. Overview of Trial Design

This is an open label, non-pharmacological, multicenter, randomized pilot study. Data will be collected on RAIR follicular cell-derived TC patients being treated with KIs as per clinical practice in multiple Institutions across Italy. The protocol was approved by the Ethics Committee (Unicamillus, Rome E00114-2025). The enrollment of patients will start after the protocol approval from the ethics committee of each center, and will continue until the target sample size has been achieved (see below). The site personnel will capture all the data (epidemiological, clinical, pathological and biochemical) electronically at the study site in an Excel database provided by the coordinating center.

The MI supplement will be shipped to the hospital pharmacy of the coordinating center and satellite centers. The product will be delivered by the pharmacy to the investigator at each center, who will then dispense it to the patients enrolled in the MI treatment group. The product can be stored at room temperature.

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Clinical and disease-related features, including gender, age at randomization, age at diagnosis of cancer, histological type, TNM stage, number and dimension of target lesions, type of metastatic site, somatic molecular mutation will be collected. History of previous treatments for thyroid cancer such as type of surgical treatment, radiotherapy and other chemotherapy/KI therapies will be collected. Quality of life (Qol) will also be assessed.

2.2. Eligibility Criteria and Study Design

Patients meeting the eligibility criteria described in Table 2 will be included. In summary, RAIR follicular cell-derived TC patients will need to have had NGS analysis for possible mutations. Eligible patients can have a BRAF mutation (treated with sKIs) or no mutations or non-targetable mutations (treated with mKIs). Patients must have been taking KIs for at least four months.

All patients will need to give their written informed consent to be included in the study.

The trial design is summarized in Figure 1. Patients will be divided into 2 groups: a) a control group in which patients are treated with KIs (T plus D or L); b) a group, in which patients are treated with the same KI and in addition with MI.

MI has a half-life of less than 24 hours, and a complete steady state can be achieved in about 4-5 days. However, a longer administration (30 days) will help ensure an effect on the various metabolic activities. After 30 days of MI treatment, all patient, treated with L-T4 at a semi-suppressive dosage as per clinical practice, will be stimulated with recombinant human TSH (rhTSH) (days 31 and 32). Then at day 35 patients will be submitted to whole-body scintigraphy, with hybrid imaging where possible (SPECT/TC), after administration of the diagnostic activity (185-222 MBq) of 123-I in accordance with the SNMMI/EANM guidelines (1). Blood samples will be collected before starting MI therapy (day 0), after 30 days of MI therapy and then at days 31, 32, 33, 34 and 35 after MI therapy. The laboratory assessments are reported in Table 3. QoL will be assessed at beginning of the MI treatment and at the end of its administration.

Patients will be withdrawn from the study if they experience any side effects from the MI or if they experience adverse unmanageable effects of the KIs, although no known side effects of MI have been reported to date.

The study will be terminated early if there is premature evidence of superiority in the MI group. The study will conclude upon evaluation of the primary endpoint.

2.3. Sample Size and Procedure

We estimate that the difference between the two percentages of subjects in terms of iodine uptake at the end of treatment would equal 30% (for example, 60% in the experimental group and 30% in the control group). We also set the alpha error and power at 5% and 80%, respectively. Given these conditions, 42 patients per group would be necessary for the effect size indicated above to lead to a statistically significant result. A total of 84 patients would therefore need to be enrolled

The patients will be enrolled with a 1:1 ratio in either the control (KI group) or treatment MI (KI plus MI) groups. The randomization list will be generated using Excel. We will include RAIR follicular cell-derived TC patients being treated with KIs as per clinical practice. The enrolled patients will be divided into groups based on the KI type and then into two subgroups: (KI only vs KI plus MI). All patients will need to give their written informed consent to be included in the study. If not already available for all patients, an NGS molecular panel will be performed to look for somatic mutations. Each patient will be identified by a two-digit code and patient initials which are the only identification elements and will only be used for the purposes of the study. Clinical data will be collected during the randomization, the first (Day 1) and last day (Day 30) of the supplementation with MI (both in the KI and KI plus MI group) and then on the day of the whole-body scintigraphy (Day 35).

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2.4. Study Aims

The objective of the study is to evaluate the efficacy of 2 g MI twice a day in RAIR follicular cell-derived TC in inducing the re-uptake of the 131I in patients during KI therapy. Although evaluation of the effectiveness of the chronic treatment of KIs on re-differentiation is not one of the end points of the study, some speculations will be possible as discussed below.

The primary endpoint is to evaluate the restoration of the 123 uptake in RAIR follicular cell-derived TC patients already on KIs therapy alone and on KIs therapy plus MI. Restoration of the 123 uptake will be evaluated in target lesions. In the case of multiple lesions, only a re-uptake in a target lesion will be considered. A regional target/background ratio of more than 4 and a 2-fold higher iodine uptake than the mean uptake in liver parenchyma by visual assessment will be considered as responders.

The secondary endpoint is to 1) evaluate the thyroglobulin trend as a secondary marker of differentiation, 2) evaluate the safety and the quality of life of these patients.

Safety will be assessed by the clinical symptoms and the laboratory parameters. This includes the monitoring of adverse events as defined in Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All investigators involved in the study will be responsible for reporting all adverse events occurring during the study.

2.5. Data Collection

Demographic data, such as age, gender, race, ethnicity, medical history, TNM stage at initial diagnosis, metastatic disease status, type of metastatic site and number of organ metastases will be collected and recorded. Data on TNM, pathological subtype and somatic molecular mutations will also be collected. History of previous treatments for thyroid cancer, such as type of surgical treatment, radiotherapy, other KI therapies or other specific treatments (embolization, chemoembolization, thermal ablation) will be collected. Laboratory data will be also collected on a prespecified day of the study (see Table 3).

Data on adverse events will also be collected and recorded according to CTCAE v5.0. The minimum information required is:

- data onset;
- the degree of the event's severity;
- if the adverse event is serious;
- causality with the drugs;
- any other medical interventions performed by the investigator.

The site personnel will capture all data electronically at the study site in an Excel database provided by the coordinating center.

3. Discussion

In this trial we will evaluate the potential role of the addition of MI to treatment with KIs (sKIs and mKIs), in restoring IU. From a practical point of view, we decided to investigate the most commonly used drugs: D plus T for BRAFV600E mutated cancer and L for BRAF WT or other non-targetable mutated cancers.

As is well-known, IU is only the first step in the therapeutic effect of RAI. The balance among IU, iodine organification and iodine leak or its secretion in thyroid hormones, determines the residence time inside the thyroid cells, and hence the final action of RAI action in terms of Gy delivered to the tissue. However, IU represents the first essential step for RAI treatment.

In our protocol, to simplify the study, we decided only to investigate IU. From an ethical point of view we may of course administer RAI therapy in patients in which we find significant IU in lesions that previously showed no uptake, and subsequently we will be able to investigate the effects of this treatment.

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In the past various substances and drugs (23–26) which appeared to increase IU did not produce clinical effects, however robust literature shows that the increase in IU by KIs can have benefits on tumor mass in a percentage of cases.

The novel features of our trial are thus the following.

Firstly, to the best of our knowledge this is the first study which explores the possible role of MI to potentiate the re-differentiation of KIs in TC and the potential synergistic effects of MI. In addition, MI is a nutraceutical agent and is virtually free of side effects and this is of special importance for oncological patients. Some studies also suggest improvements in the quality of life in patients treated with MI. The double arm in this study will enable us to understand the respective roles of KIs alone and KIs plus MI.

In the protocol we need to tackle the issues regarding the dose of MI and the time of administration. MI has a half-life of about 24 hours, may thus reach a steady state after 4-5 days. However, we preferred a more prolonged administration period to enable the optimal incorporation of MI in the plasma membrane. Another important aspect concerns the dosage. According to the literature, a 4-gram dose of MI shows significant clinical efficacy across different pathological conditions (27). This is also the maximum dose allowed by the Italian Ministry of Health for use as a nutraceutical (https://www.salute.gov.it/new/sites/default/files/imported/C_17_pagineAree_1268_4_file.pdf). It is worth noting, however, that several studies have also demonstrated the effectiveness of MI at lower doses, particularly in the management of thyroid disorders (28–30).

In the present study, we will include α-lactalbumin in the supplement alongside MI, as this prebiotic molecule plays an important role in enhancing the intestinal absorption of myo-inositol through the gap junctions of enterocytes (31).

In addition to adding MI to the KI treatment, which is the main aim of our investigation, our protocol has several differences compared to previous protocols on the re-differentiation of TC by KIs.

In most protocols, KIs were administered for re-differentiation purposes only when the tumor was in progression and RAI uptake was investigated shortly afterwards. For this reason, in some cases, the final clinical effects (KI itself Vs RAIT) on tumor mass and progression were not clearly separable.

In our protocol patients have already been on treatment with KIs for a reasonably long time, and thus any subsequent clinical effect of RAIT, in patients with restored IU, would be without doubt due to the effect of the latter. We decided to investigate not only patients on KI treatment with stable disease but also patients on KI treatment who experience progressive disease. We realize that these patients theoretically have a low chance of having restored IU. However no paper has investigated whether inhibition growth and IU could be separate effects of KIs.

The investigation of the effect of the therapy with L is another novelty since to date few studies have investigated mKIs as re-differentiating agents.

As secondary end points we will consider unstimulated Tg values. Some literature data show that Tg can increase together with the re-differentiation (15). It would thus be interesting to evaluate the behavior of Tg as a surrogate of re-differentiation in KIs alone and KIs plus MI.

The other secondary end point is the QoL. As already stated, as a general presupposition, MI should not impact negatively on the QoL of patients. There are some data on the use of MI on hypothyroidism, and the complex effects of MI on metabolism could be of help in these fragile patients. In fact we would expect some beneficial effects on the patients' well- being.

In the future it would be interesting to also evaluate whether several months of treatment with KIs could improve the possibility of inducing re-differentiation. Our aim was not to have a further control group in which KI was added when the disease progresses and just before radioiodine treatment as in the previous studies. However indirect comparisons could be made with previous works.

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4. Conclusions

The study evaluates the possible re-differentiation of iodine refractory thyroid cancer in patients treated with KIs plus MI. The re-uptake of iodine will be evaluated as the primary end point, and Tg values and QoL will be evaluated as the secondary end points. The main limitation of the study is that we do not investigate any clinical effects. However, we will have to post-pone the clinical analysis to a later date after the administration of RAI for therapeutic purposes. The choice of 123 I was just to prevent the stunning effect. We believe that this study presents novel aspects that could lead to new forms of treatment.

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