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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS BIOLÓGICAS:
FARMACOLOGIA E TERAPÊUTICA

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EFEITO DOS INIBIDORES MULTIQUINASE NA TERAPIA DE REPOSIÇÃO DE LEVOTIROXINA EM PACIENTES COM CARCINOMA DE TIREOIDE

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Elaborada por

GRAZIELA CRISTINE GOERCK

Como requisito parcial para a obtenção do título de Mestre em Farmacologia e Terapêutica

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RESUMO

Introdução: Os inibidores de multiquinase (IMK) têm sido utilizados no tratamento do câncer de tireoide (CT) avançado. Em pacientes recebendo terapia de reposição com levotiroxina, o IMK pode aumentar a necessidade de hormônio da tireoide.**Objetivo:** Investigar os efeitos do IMK na terapia de reposição com hormônio tireoidiano em uma coorte de pacientes com CT. **Metodologia:** Foram incluídos pacientes com CT em uso de IMK acompanhados em um centro de referência. Para os pacientes com câncer diferenciado de tireoide (CDT), o objetivo do tratamento era atingir níveis séricos de TSH < 0,1 mUI/mL. Para os pacientes com câncer medular de tireoide (CMT), o objetivo da reposição era manter os níveis sérios de TSH dentro da faixa de valores normais (0,35-4,9 mUI/mL). A dose inicial de levotiroxina foi calculada considerando o peso do paciente (mcg/kg) e posteriormente ajustada para atingir esses objetivos. A dose de levotiroxina antes do início do IMK foi considerada a dose basal e a dose máxima durante o uso do IMK foi considerada a dose máxima. **Resultados**: Foram incluídos 26 pacientes, 11 (42,3%) com CDT e 15 (57,7%) com CMT. O tratamento com IMK de primeira linha para CDT foi sorafenibe e para CMT foi vandetanibe. A duração média do uso de IMK foi de 21 meses (P25-75 11-49) e todos os pacientes tiveram pelo menos um efeito colateral, sendo as reações cutâneas o efeito mais comum (80,7%). Após uma mediana de 12 meses (P25-75 8-20) do uso de IMK, 23 pacientes dos 25 analisados (92%) necessitaram de algum incremento na dose de reposição de levotiroxina com um aumento mediano de 38% (P25-75 18-57). Os fatores de risco para elevação mais proeminente da dose de levotiroxina foram idade mais jovem, uso mais prolongado do IMK e maior número de sítios com metástases. **Conclusão**: A maioria dos pacientes com CT que utilizam IMK necessitam de aumento da dose de reposição de levotiroxina. Portanto, o monitoramento da reposição com levotiroxina deve ser feito com cuidado nesse grupo de pacientes, com aferições mais frequentes dos níveis de TSH especialmente nos pacientes mais jovens, com maior tempo de uso do IMK e doença mais extensa.

Palavras-chave: inibidor multiquinase , vandetanibe, levantinibe, sorafenibe, carcinoma medular de tireoide, carcinoma diferenciado de tireoide, CDT, CMT.

ABSTRACT

Introduction: Multikinase inhibitors (MKI) have been used to treat advanced thyroid cancer (TC). In patients receiving levothyroxine replacement therapy, MKI may increase the need for thyroid hormone. **Objective**: To investigate the effects of MKI on thyroid replacement therapy in a cohort of TC patients. **Methodology**: Patients with TC using MKI followed in a referral center were included. For those patients with differentiated thyroid cancer (DTC), the goal of TSH was <0.1 mIU/mL and for those with medullary thyroid cancer (MTC), the normal range of TSH values (0.35-4.9 mIU/mL). Initial levothyroxine dose was calculated considering the patient weight (mcg/kg) and adjusted to reach these goals. The dose of levothyroxine before the start of MKI was considered the basal dose and the maximal dose during the MKI use was the maximal dose. **Results**: 26 patients were included, 11 (42.3%) with DTC and 15 (57.7%) with MTC. First-line MKI treatment for DTC was sorafenib and for MTC was vandetanib. The mean duration of MKI's use was 21 months (P25-75 11-49) and all patients had at least one side effect, being the most common skin reactions (80.7%). After a median of 12 months (P25-75 8-20) of MKI's use, 92% (n=23) needed increases on the levothyroxine replacement dose with a median dose increase of 38% (P25-75 18-57). Risk factors for more prominent elevation in levothyroxine dose were younger age, longer use of MKI treatment and more sites of distant metastasis. **Conclusion**: The majority of TC patients using MKI need increases in the levothyroxine replacement dose. The monitoring should be done carefully with more frequents TSH dosages in those patients with younger age, longer time on MKI and more extensive disease.

Key-words: multikinase inhibitor, vandetanib, levantinib, sorafenib, CDT, CMT

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LISTA DE ABREVIATURAS E SIGLAS

ATP	Adenosina Trifosfato
CAT	Carcinoma Anaplásico de Tireoide
CDT/DTC	Carcinoma Diferenciado de Tireoide
CFT	Carcinoma Folicular de Tireoide
CPT	Carcinoma Papilar de Tireoide
CMT/MTC	Carcinoma Medular de Tireoide
CPDT	Carcinoma Pouco Diferenciado de Tireoide
D1	Iodotironina Desiodase Tipo 1
D2	Iodotironina Desiodase Tipo 2
D3	Iodotironina Desiodase Tipo 3
DP	Doença Progressiva
DP	Desvio Padrão
ECOG	*The Eastern Cooperative Oncology Group*
EGFR	Receptor do fator de crescimento epidérmico
EMA	*European Medicines Agency*
FDA	*Food and Drug Administration*
HGFR	Receptor do fator de crescimento do hepatócito
HT	Hormônio Tireoidiano
IRA/RAI	Iodo Radioativo
MKI/IMK	Inibidor Multiquinase
NEM	Neoplasia Endócrina Múltipla
RAI-R	Radioiodo refratário
RET	*Re-arranged during Transfection*
SPSS	*Statistical Package for Social Science Professionall*
TC/CT	Tomografia computadorizada
TKI/ITK	Inibidor tirosinaquinase
TGFR	Receptor do fator de crescimento tumoral
TSH	Hormônio estimulante da tireoide
T3	Triiodo-L-tironina
T4	Tetraiodo- L -tironina
T4L	Tiroxina 4 livre
TT	Tireoidectomia total

TC	*Thyroid cancer*
TC	Tomografia computadorizada
US	Ultra sonografia
VEGFR	Receptor do fator de crescimento do endotélio vascular
WBS	*Whole-body scan* (varredura de corpo inteiro)

SUMÁRIO

1 INTRODUÇÃO

1.1 Carcinoma de Tireoide

O carcinoma de tireoide é a neoplasia maligna mais comum do sistema endócrino, cuja incidência tem aumentado nos últimos anos, sendo a população feminina a mais afetada. Estimativa realizada pelo Inca para o triênio 2020-2022 revela que anualmente são esperados 11.950 novos casos na população feminina e 1.830 na população masculina no Brasil (INCA - Instituto Nacional de Câncer - Estimativa 2020 – Brasil https://www.inca.gov.br/numeros-de-cancer). Desde a década de 1980 tem se observado um aumento na incidência do câncer de tireoide em muitos países, particularmente após a introdução de novas técnicas de diagnóstico (ultrassonografia) (VACCARELLA et. al., 2016).

Os tipos de carcinomas da tireoide são classificados de acordo com as suas características histológicas: carcinoma diferenciado (CDT) englobando o carcinoma papilar (CPT) e carcinoma folicular (CFT), carcinoma indiferenciado (anaplásico) (CAT) e carcinoma medular (CMT) (DELELLISA et al., 2004).

O carcinoma diferenciado de tireoide (CDT) tem origem na célula folicular tireoidiana e é o mais comum dos carcinomas da tireoide, representando mais de 90% dos tumores da glândula e compreendendo o carcinoma papilar de tireoide (CPT) e o carcinoma folicular de tireoide (CFT) (HEQING, 2017). O tipo de carcinoma anaplásico de tireoide representa somente cerca de 1% dos tumores tireoidianos, podendo se originar de novo ou ser resultado da progressão e/ou desdiferenciação dos CDTs (JANJUA; WREESMANN, 2018).

O CDT tem um prognóstico relativamente bom, mas a presença de metástases à distância pode levar à morte por doença progressiva (DP). Estes pacientes com doença mais extensa em geral são tratados incialmente com tireoidectomia e terapia com radioiodo. No seguimento, uma outra estratégia terapêutica utilizada é a supressão do hormônio estimulante da tireoide (TSH) com doses elevadas de levotiroxina (IWASAKI et al, 2019). Essa terapia tem como base o fato de que as células tumorais expressam o receptor do TSH na membrana celular e o TSH estimula a taxa de crescimento celular (YOON et al., 2019). Dessa forma, a supressão do TSH tem como objetivo diminuir a chance de doença persistente/recorrência nestes pacientes.

Já o carcinoma medular de tireoide (CMT) é originado das células C ou parafoliculares da tireoide e representa até 5% dos tumores tireoidianos (WELLS et al., 2015, CARHILL et al., 2013, TSANG, 2019). O CMT pode ocorrer na forma hereditária/familiar (25% dos casos) ou esporádica (75% dos casos). Na forma familiar, o CMT é um dos componentes da síndrome genética Neoplasia Endócrina Múltipla Tipo 2 (NEM 2). A forma mais comum desta síndrome é a NEM 2A, caracterizada pela presença de CMT (95%), feocromocitoma (50%) e hiperparatireoidismo (20%). A NEM 2B inclui, além do CMT (90%), a presença de feocromocitoma (45%), ganglioneuromatose (100%), habitus marfanoide (65%) e anormalidades oculares (nervos da córnea espessados, conjuntivite seca e inabilidade de chorar com lágrimas). Já a forma de CMT esporádica é definida pela presença isolada de CMT (FERREIRA et al, 2013, MAIA, 2014). O CMT habitualmente é um tumor de crescimento lento, mas que pode estar associado à doença metastática no momento do diagnóstico (ANTONELLI et al., 2012). A metástase mais comum apresenta-se nos gânglios linfáticos do pescoço, podendo também disseminar-se para o pulmão, fígado e osso (ALMEIDA; HOFF, 2012).

A maioria dos pacientes com CMT apresenta um nódulo no pescoço ou metástase à distância. Os nódulos podem ocasionalmente apresentar algum sintoma como disfagia (dificuldade ou desconforto na deglutição) ou disfonia (dificuldade para falar). Outros sintomas também podem estar relacionados ao efeito de metástases, especialmente diarreia, rubor, dispneia e dor óssea (VIOLA; ELISEI, 2019, TAPPENDEN et al., 2019). Segundo Tappendem et al, os pacientes diagnosticados com CMT podem ser classificados da seguinte forma: pacientes com doença localizada sem evidência de metástases, nos quais a cura cirúrgica é possível; pacientes com doença metastática limitada ao pescoço, nos quais a cura cirúrgica pode ser possível, mas nem sempre é alcançada; e pacientes com metástase à distância, nos quais a cirurgia não é curativa.

A maioria dos casos diagnosticados de CMT acontece nos pacientes com idade entre a quarta e quinta década, porém observam-se casos em faixas bem amplas de idade (VIOLA; ELISEI, 2019).

A patogênese do carcinoma de tireoide é um processo de múltiplos passos que envolve de um lado, mutações genéticas tanto em oncogenes, como em genes supressores de tumores, causando proliferação celular anômala, e de outro lado, alterações de genes

envolvidos na angiogênese, essenciais para a invasão local e metastática (MATRONE et al., 2017).

A Tireoidectomia Total (TT) é o tratamento usual de todos os carcinomas de tireoide, seguida do tratamento com radioiodo em CDT. Os principais casos de óbito relacionados ao câncer de tireoide são os de CDT cirurgicamente inoperável e refratário a radioiodo, CPDT e CAT. Uma questão primordial do tratamento desses tipos de câncer de tireoide é equilibrar os benefícios associados ao tratamento com os danos associados aos efeitos adversos do tratamento (XING; HAUGEN; SCHLUMBERGER, 2013).

1.2 Inibidores de multiquinases (IMKs)

Nos últimos anos descobertas sobre as diferentes vias de sinalização e anormalidades genéticas do carcinoma de tireoide permitiram um melhor entendimento da patogênese dessa doença. A partir disso, foi possível o desenvolvimento de terapias moleculares mais específicas, dentre elas destacam-se os inibidores de multiquinases (IMKs) (ANTONELLI et al., 2012). Esses fármacos são pequenas moléculas que competem com a adenosina trifosfato (ATP), inibindo a autofosforilação e a transdução através de diferentes vias de sinalização (MAROTTA et al., 2015). As tirosina quinases funcionam como intermediários de sinalização, estimulando a proliferação tumoral, angiogênese, invasão, metástase e autorregulação celular e afetam tanto a regulação das células cancerígenas, como das células não cancerígenas. Os IMKs atuam inibindo a atividade quinase do receptor do fator de crescimento epidérmico (EGFR), do receptor do fator de crescimento do endotélio vascular (VEGFR), do receptor RET-TK, do receptor do fator de crescimento tumoral (TGFR), do receptor do fator de crescimento do hepatócito (HGFR), entre outros (RODRIGUES, 2006).

Esse grupo de fármacos têm sido um foco de interesse no tratamento do câncer de tireoide desde a descoberta dos papéis oncogênicos de mutações em serina quinase BRAF, tirosina quinases RET e RAS e de sua capacidade de inibir receptores de fator de crescimento, como o VEGFR (MATRONE et al., 2017; VALERIO et al., 2017). Atualmente, o uso dos IMKs está indicado para pacientes com CDT avançado e progressivo refratário ao radioiodo ou CMT com doença metastática localmente progressiva ou distante, e/ou doença sintomática que não pode ser tratada com cirurgia ou abordagens locais (PITOIA et al., 2018).

Nesta classe de medicamentos, atualmente temos disponível no Brasil, três fármacos aprovados para uso em pacientes com carcinoma de tireoide avançado: vandetanibe, tosilato de sorafenibe e lenvatinibe.

O vandetanibe é um inibidor oral do VEGFR-2 e 3, das tirosinas quinases do RET e, em concentrações mais elevadas, do EGFR (SHERMAN, 2009; TAPPENDEN et al., 2019). Estudos demonstraram que o vandetanibe pode constituir uma terapêutica eficaz para os pacientes com CMT avançado, uma vez que permite aumento da sobrevida livre de progressão e possui um perfil de efeitos adversos tolerável (WELLS et al., 2010; ROBINSON et al., 2010). A administração do vandetanibe é feita por via oral e a dose recomendada de 300 mg uma vez por dia (TAPPENDEN et al., 2019).

O sorafenibe têm como alvo terapêutico o VEGFR-1, 2 e 3, RET, RAS, BRAF, PDGFR (receptor do fator de crescimento derivado das plaquetas), c-KIT e Flt-3 e também tem atuação na apoptose, autofagia, antiproliferação e inibição da regulação da angiogênese. Antes de ser aprovado para tratamento de carcinoma de tireoide já estava em uso em outras neoplasias, especialmente o carcinoma hepatocelular irressecável e o carcinoma de células renais avançado. Este medicamento tem demonstrado aumento da sobrevida livre de progressão em pacientes com CDT e a dose terapêutica recomendada é de 400 mg duas vezes ao dia (CAPDEVILA et al., 2012; MATRONE et al., 2017).

O lenvatinibe é um medicamento que atua como inibidor do VEGFR-1, 2 e 3, FGFR, PDGFR, c-KIT e do RET (Liebner DA, 2011; Perez CA, 2012; Matrone A et al, 2017). Com base nos resultados de ensaio clínico de fase III, o lenvatinibe foi aprovado pela FDA e EMA em 2015 para o tratamento de pacientes com CDT avançado e progressivo refratário a iodo (MATRONE et al., 2017).

Os inibidores de multiquinases apresentam diversos efeitos colaterais como: hipertensão, diarreia, rash cutâneo, anorexia, náusea, perda de peso, fadiga e prolongação do intervalo QT no eletrocardiograma (VALERIO et al., 2017), além de induzirem hipotireoidismo, sendo frequentemente necessário aumentar a dose de levotiroxina e monitorizar regularmente a função tireoidiana (CARHILL, 2013). Estudo realizado por Kim et al. (2019), observou algumas diferenças importantes nos perfis de segurança do uso de lenvatinibe e do sorafenibe. A incidência de reação cutânea mão-pé, alopecia e erupção cutânea de qualquer grau foi significativamente menor em pacientes tratados com lenvatinibe em comparação com aqueles tratados com sorafenibe. Porém a incidência de hipertensão, prolongamento do intervalo QT e proteinúria de qualquer grau foi significativamente maior em pacientes tratados com lenvatinibe em comparação com aqueles tratados com tosilato de sorafenibe.

Além disso, foram relatados efeitos adversos raros como: insuficiência cardíaca, trombocitopenia e carcinoma espinocelular durante a terapia com sorafenibe e carcinoma espinocelular e ooforite com perfuração intestinal durante o tratamento com vandetanibe (PITOIA et al., 2018).

1.3 Hipotireoidismo

O hipotireoidismo primário refere-se a uma diminuição da produção do hormônio pela tireoide, o que provoca um aumento nos níveis de TSH acima do normal, sendo a causa mais frequente a tireoidite autoimune crônica. Os sintomas característicos do hipotireoidismo incluem fadiga, ganho de peso, intolerância ao frio, entre outros (BRENTA et al., 2013).

Nos pacientes com carcinoma de tireoide, o tratamento inicial sempre é a remoção cirúrgica da glândula tireoide (tireoidectomia). Dessa forma, estes pacientes sempre estarão em hipotireoidismo e parte do tratamento e seguimento desses pacientes é a reposição dos hormônios tireoidianos a partir da levotiroxina.

Para pacientes com CDT, é indicado o uso de doses mais elevadas de tiroxina para manter TSH mais baixo do que o normal (tratamento supressivo) como uma das estratégias para diminuir risco de recidiva e eventos desfavoráveis.

Como visto anteriormente, os pacientes com indicação para tratamento com IMKs são aqueles que apresentam doença avançada: doença persistente estrutural não tratável com outra modalidade de tratamento e em progressão. Em geral, estes pacientes já foram submetidos a diversos tratamentos para o carcinoma de tireoide, incluindo a tireoidectomia. Logo, todos eles estão em tratamento para reposição de levotiroxina. Com o uso destes fármacos, observa-se a necessidade de aumento significativo da dose de levotiroxina, o qual pode ser evidenciado pela elevação dos níveis de TSH.

Estudo utilizando 21 diferentes inibidores tirosina quinase (ITK) em pacientes com câncer não tireoidiano demonstrou que aproximadamente 40% dos pacientes desenvolveu hipotireoidismo durante ou após seis meses do tratamento com ITK (LECHNER et al., 2018). Esses dados são importantes, pois demonstram que o aumento das doses de levotiroxina independem de haver uma doença na tireoide prévia, sendo que a função tireoidiana deve ser uma prática no seguimento dos pacientes que utilizam esse tipo de medicamentos.

Outro estudos utilizando o medicamento Vandetanibe no tratamento de CMT observaram que em 78% dos pacientes versus 21% nos pacientes com placebo tiveram aumento dos níveis de TSH, resultando em aumento da dose de reposição de hormônio tireoidiano em 49,3% dos pacientes tratados com vandetanibe versus 17,2% placebo (CAMPBELL; SEIB; GOSNELL,2013).

Miyake et al. (2010) demonstraram que em 67,7% dos pacientes com câncer de células renais em uso de torsilato de sorafenibe, houve desenvolvimento de hipotireoidismo. Com relação às características dos pacientes, o único fator que contribui para o desenvolvimento de perda da função tireoidiana foi a idade avançada (MIYAKE et al., 2010).

Vários estudos também mostraram que o hipotireoidismo é um efeito adverso comum da terapia com ITK do receptor do fator de crescimento endotelial vascular (VEGFR-TKI). Os mecanismos propostos incluem regressão capilar do tecido tireoidiano, bloqueando o VEGFR e o receptor do fator de crescimento derivado de plaquetas (PDGFR), biossíntese reduzida do hormônio tireoidiano, inibindo a captação de peroxidase e iodo, transporte transmembranar de doenças tireoidianas dos hormônios derivados e aumento da desiodação do tipo 3 (BAILEY et al., 2015).

Apesar desta observação ser frequente não há na literatura explicação para este fenômeno, nem mesmo quantificação ou caracterização do mesmo. Possíveis explicações seriam efeitos desses fármacos sobre as iodotironinas, enzimas muito importantes no metabolismo dos hormônios tireoidianos, e que podem estar envolvidas nos mecanismos que levam à desregulação dos hormônios tireoidianos causada pelo tratamento com estas drogas.

2 JUSTIFICATIVA

Os IMKs são uma nova e promissora classe de fármacos para o tratamento do carcinoma de tireoide avançado. Além da demonstrada eficácia em prolongar a sobrevida livre de progressão destes pacientes, é frequentemente observado no seguimento destes pacientes, a necessidade de um aumento da dose de reposição de levotiroxina para manter os níveis de TSH dentro dos alvos terapêuticos. No entanto, este fenômeno não está bem caracterizado, nem mesmo quantificado nos pacientes com CT. Da mesma forma, para que seja possível uma boa aderência e resultado com o uso desses medicamentos é importante que os efeitos adversos sejam entendidos e manejados possibilitando uma melhor qualidade

de vida dos pacientes. Portanto, a caracterização do efeito desses medicamentos sobre o tratamento do hipotireoidismo constitui uma medida essencial no uso desta nova arma terapêutica.

3 OBJETIVOS

3.1 Objetivo geral

Investigar os efeitos dos IMKs na necessidade de reposição de levotiroxina e descrever o seu uso em uma coorte de pacientes com carcinoma de tireoide em acompanhamento em um centro de referência.

3.2 Objetivos específicos

- Descrever e identificar os fatores preditores de aumento da necessidade de levotiroxina nos pacientes tireoidectomizados em uso de IMK;
- Descrever o uso dos IMK em uma coorte pacientes com carcinoma de tireoide: indicação, extensão da doença, resposta ao tratamento, desfechos;
- Identificar e descrever os principais efeitos adversos nos pacientes tratados com IMK;
- Correlacionar os achados acima com tipo de câncer, extensão da doença e resposta ao tratamento.

4 ARTIGO CIENTÍFICO

EFFECTS OF MULTIKINASE INHIBITORS TREATMENT ON LEVOTHYROXINE REPLACEMENT THERAPY IN THYROID CANCER PATIENTS

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ABSTRACT

Introduction: Multikinase inhibitors (MKI) have been used to treat advanced thyroid cancer (TC). In patients receiving levothyroxine replacement therapy, MKI may increase the need for thyroid hormone.

Objective: To investigate the effects of MKI on thyroid replacement therapy in a cohort of TC patients.

Methodology: Patients with TC using MKI followed in a referral center were included. For those patients with differentiated thyroid cancer (DTC), the goal of TSH was <0.1 mIU/mL and for those with medullary thyroid cancer (MTC), the normal range of TSH values (0.35-4.9 mIU/mL). Initial levothyroxine dose was calculated considering the patient weight (mcg/kg) and adjusted to reach these goals. The dose of levothyroxine before the start of MKI was considered the basal dose and the maximal dose during the MKI use was the maximal dose.

Results: 26 patients were included, 11 (42.3%) with DTC and 15 (57.7%) with MTC. First-line MKI treatment for DTC was sorafenib and for MTC was vandetanib. The mean duration of MKI's use was 21 months (P25-75 11-49) and all patients had at least one side effect, being the most common skin reactions (80.7%). After a median of 12 months (P25-75 8-20) of MKI's use, 92% (n=23) needed increases on the levothyroxine replacement dose with a median dose increase of 38% (P25-75 18-57). Risk factors for more prominent elevation in levothyroxine dose were younger age, longer use of MKI treatment and more sites of distant metastasis.

Conclusion: The majority of TC patients using MKI need increases in the levothyroxine replacement dose. The monitoring should be done carefully with more frequents TSH dosages in those patients with younger age, longer time on MKI and more extensive disease.

INTRODUCTION

Thyroid cancer is the most common malignant neoplasm of the endocrine system and its incidence has increased in recent years, with the female population being the most affected. The thyroid carcinomas are classified according to their histological characteristics as differentiated carcinomas (DTC), including papillary carcinoma (PTC) and follicular carcinoma (FTC); medullary carcinoma (MTC); poorly differentiated carcinoma; and anaplastic thyroid carcinoma (CARHILL et al., 2013).

DTC and MTC patients often have an excellent prognostic and these tumors usually are characterized as slow-growing tumors (SCHEFFEL et al., 2015). A minority of the patients can show metastatic site during the disease and the most common metastasis site is in the lymph nodes of the neck. Distant metastases occur in 5-10% of these patients and the most common sites are lung, liver and bones (ALMEIDA; HOFF, 2012).

The pathogenesis of thyroid cancer is a process of multiple steps which involves on the one hand, genetic mutations both on oncogenes and in tumor suppressive genes, causing anomalous cellular proliferation and on the other hand, changes in genes involved in angiogenesis, essential for local and metastatic invasion (MATRONE et al., 2017). In recent years there have been several discoveries signaling different pathways and genetic abnormalities involved in the pathogenesis of thyroid cancer. From this, it was possible to develop more specific molecular therapies, among them the tyrosine kinase inhibitors (ANTONELLI et al., 2012). These drugs are small molecules that compete with adenosine triphosphate (ATP), inhibiting autophosphorylation and transduction through different signaling pathways (MAROTTA et al., 2015). They act by inhibiting the activity of epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGFR), transmembrane receptor tyrosine kinase (RET-TK), tumor growth factor (TGFR), hepatocyte growth (HGFR), among others (NAVA et al., 2019).

In this class of medications, we currently have three drugs approved to be used in patients with advanced thyroid cancer: vandetanib, sorafenib and levantinib (RODRIGUES A; 2006, WELLS et al., 2010, ROBINSON et al., 2010). Vandetanib is an oral inhibitor of VEGFR-2 and 3, RET and, at higher concentrations, EGFR (SHERMAN, 2009). Studies have shown that vandetanib can be an effective therapy for patients with advanced MTC as it allows for increased progression-free survival and a bearable adverse effect profile

(WELLS et al., 2010, ROBINSON et al., 2010). Sorafenib, has as the therapeutic target VEGFR-1, 2 and 3, RET (including RET/PTC), RAS, BRAF RAF (including BRAF V600E), the receiver of the platelet derived growth factor (PDGFR), c-Kit and Flt-3 and also acts on apoptosis, autophagia, antiproliferation and inhibition of angiogenesis regulation. Before being approved for treatment of thyroid cancer, it was already being used in other neoplasms, especially hepatocellular carcinoma and renal cell carcinoma. This medicinal product has demonstrated increased progression-free survival in patients with DTC (CAPDEVILA et al., 2012; MATRONE et al., 2017). Levantinib is an inhibitor of VEGFR-1, 2 and 3, FGFR α, PDGFR, c-KIT and RET (MAROTTA et al., 2015; PEREZ et al., 2011; MATRONE et al., 2017). Based on the results of the phase III clinical trial, levantinib was approved by the FDA and EMA in 2015 for the treatment of patients with advanced and progressive iodine refractory DTC (MATRONE et al., 2017).

MKIs have several side effects such as hypertension, diarrhea, skin rash, anorexia, nausea, weight loss, fatigue, and a prolonged QT interval on the electrocardiogram (VALERIO et al., 2017). An interesting observation is that this class of drugs may induce hypothyroidism, which is thought to be associated with poor absorption of levothyroxine due to either decreased absorption from secondary causes such as diarrhea or increased clearance. In those patients using levothyroxine replacement therapy, they may to increase the levothyroxine dosage and to regularly monitor thyroid function (CARHILL et al., 2013).

Since in patients diagnosed with thyroid cancer the initial treatment is surgical removal of the thyroid gland, these patients will always have hypothyroidism and part of the treatment and follow-up of these patients will be levothyroxine replacement therapy. This is critical in patients with advanced DTC, since the use of higher doses of levothyroxine to maintain thyroid-stimulating hormone (TSH) lower than normal (suppressive treatment) is one of the strategies to decrease risk of unfavorable events and relapse (LEE; JEON; KIM, 2019). Another important aspect is that the symptoms of hypothyroidism can negative impact the quality of life of these patients, especially those with advanced disease.

Therefore, the adequate control of hypothyroidism in thyroid cancer patients is an essential aspect of the treatment and the knowledge of the impact of the use of MKIs on the need of levothyroxine replacement could have important prognostic implications. Here, we describe the use of MKI in a cohort of thyroid cancer patients treated at a referral center and investigate the effects of MKIs on hypothyroidism treatment.

MATERIAL AND METHODS

Patients and study design

The patients included were followed in a cohort of thyroid cancer patients from the Thyroid Unit, Endocrine Division, of Hospital de Clínicas de Porto Alegre (HCPA), a tertiary care, university teaching hospital in southern Brazil. From 2011 to April 2019, all consecutive patients with a histological diagnosis of thyroid cancer and treated with MKI (vandetanib, sorafenib or levantinib) were included. All data were retrospectively obtained from patients' medical records. The study was approved by the ethics committee of the institution (CAAE 93280918500005327 / GPPG 2018-0399).

Treatment protocol and follow-up

Our DTC treatment protocol consists of performing total thyroidectomy, followed or not by administration of radiodine (RAI) as indicated, and use of suppressive levothyroxine therapy according to current guidelines (HAUGEN et al., 2016). The iodine administration protocol used RAI activities prescribed at the attending physician's discretion. RAI was administered in a stimulated thyrotropin (TSH) condition of endogenous hypothyroidism (TSH >30 mUI/L), after withdrawing levothyroxine (at least 3-4 weeks). A post-therapy whole body scan (WBS) was performed seven to ten days after the RAI administration.

In the first evaluation, the following data were recorded for each patient: demographics, tumor characteristics (e.g., histological features, extension and lymph node involvement) and treatment (e.g., surgery, RAI, and other interventions). Each patient was classified using the 8th edition of the TNM/AJCC (TNM8) staging system (I, II, III, or IV) (TUTTLE; HAUGEN; PERRIER, 2017). No status was determined by clinical examination of the neck or pre- and postoperative neck US imaging or macroscopic examination during surgery and pathological examination of patients with lymph node resection.

The follow-up protocol called for an initial assessment at three to six months post surgery, which included a physical examination of the neck and measurements of serum tumor markers (thyroglobulin in DTC and calcitonin and CEA in MTC). Neck ultrasound (US) was also performed during the first year of follow-up. Patients classified as disease free

were scheduled for annual visits that included a physical examination of the neck and measurements of tumor markers. Patients with persistent disease were scheduled for medical visits twice a year and evaluated for additional therapy as needed. Additional imaging studies (e.g., neck US, diagnostic 131I whole-body scan [WBS], and computed tomography [CT]) were performed as indicated when clinical or laboratory findings raised suspicion of persistent or recurrent disease. Duration of follow-up was defined as the time between the TT and the last medical visit to the clinic.

Multikinase inhibitors treatment protocol

The indications of treatment with MKI were for DTC patients was RAI refractory (RAI-R) disease with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches or MTC with locally or distant metastatic disease (HAUGEN et al., 2016). Patients were classified as having RAI-R disease if they have: (i) lack of RAI uptake on post- therapy scan after RAI-administered activity >30 mCi following appropriate iodine deprivation and adequate TSH elevation; (ii) lack of RAI uptake on a properly conducted diagnostic whole-body scan in the setting of known structural disease, as demonstrated by cross-sectional imaging; (iii) structural progression of thyroid cancer 6–12 months after RAI therapy; (v) a rising Tg level 6–12 months after RAI therapy; and (vi) continued progression of thyroid cancer, despite cumulative RAI-administered activities >500–600 mCi in adult patients (SCHLUMBERGER et al., 2014). In MTC patients, the indication of MKI treatment was locally or distant metastatic disease. All patients should have symptomatic disease and progressive disease that cannot be managed with surgery or local approaches (SCHLUMBERGER et al., 2014).

All patients indicated for use of these drugs were initially assessed by their performance status using the Eastern Cooperative Oncology Group Performance Status (ECOG) (OKEN et al., 1982) and considered eligible if < 2. Physical examination was performed prior to initiation of medication and at each new appointment, with blood pressure, heart rate, cardiac and pulmonary auscultation, skin, scalp, hands, feet, weight and cervical examination. Preexisting organ dysfunction was investigated before use and at each clinical visit through laboratory tests for hematological, renal, hepatic, cardiac, urinary, pancreatic, hydroelectrolytic and coagulation disorders, tumor marker evaluation and LT4 suppression control. Imaging tests (tomography, ultrasound, magnetic resonance imaging) were

performed before the start of the drug, after 3 months and spaced to 6 months if the patient had tolerance to the drug and was considered with partial or complete response by RECIST criteria (NISHINO et al., 2010). If progression were identified during follow-up, the patient was evaluated for medication change. Clinical examinations were performed before starting the medication and every 15 days in the first month and spaced to 30 - 90 days according to medication tolerance. All patients were advised to maintain their normal diet, avoiding fats and frying; hydration of their hands and feet, use of sunscreen daily, avoid hot water on skin and use of cleaners without adequate protection.

During follow-up adverse effects were investigated and graded 0-5 (A TROTTI et al., 2003). Grade 0-2 adverse effects were managed with targeted measures for each condition without TKI dose adjustment; grade 3 halving or 3/4 dose reduction (depending on each drug being used) and the patient reassessed within 7 days. If stability the dose was maintained until complete remission of adverse effects and titrated to full dose as soon as possible. Grade 4 adverse effects required discontinuation of the drug until complete remission to avoid grade 5 and, as the case may be, return to half the dose as soon as the patient was asymptomatic.

Hypothyroidism treatment

All patients were treated with levothyroxine. For those patients with DTC, the goal of TSH was < 0.01 since all patients had metastatic disease. For those with MTC it was to maintain the patients in euthyroidism. Initial levothyroxine dose was calculated considering the patient weight (mcg/kg) and adjusted to reach these goals. The dose of levothyroxine before the start of MKI was considered the basal dose and the maximal dose during the MKI use was the maximal dose.

Statistical analysis

The clinical and laboratory data are reported as the mean ± standard deviation (SD) values or as the median and percentiles 25 and 75 (P25-75) for continuous variables, or as absolute numbers and percentages for categorical variables.

Comparative analyses of frequencies were performed using Pearson Chi-Square or Fisher's Exact Test, as appropriate. These analyses were performed using the Statistical Package for Social Science Professional software version 20.0 (IBM Corp., Armonk, NY). All tests were two-tailed, and a $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics

Twenty-six patients were included. Clinical and oncological characteristics of these patients are described in **Table 1**. The mean age at diagnosis was 51.8 ± 17.5 years and 14 (53.8%) were women. Regarding histological type, 15 (57.7%) patients had MTC, 9 (34.6%) had PTC and 2 (7.7%) had FTC. All patients had at least one distant metastasis and the majority of the patients had more than two distant metastasis (n=23, 88.5%).

All but one patient underwent thyroidectomy (the patient who did not undergo thyroidectomy was considered inoperable and used MKI as a neoadjuvant therapy for tumor reduction). Of the 15 MTC patients analyzed 9 (60%) underwent complementary radiotherapy to reduce lesions, 1 (6.6%) patient used systemic chemotherapy and 5 (33.3%) underwent additional surgery. Regarding the 11 DTC patients 9 (81.8%) patients underwent RAI, 1 (9.1%) underwent complementary radiotherapy and 2 (18.2%) underwent additional surgery.

MKI treatment

The drug used as first-line treatment for MTC patients was vandetabib, and this was used in all patients with MTC. In the group of patients with DTC, sorafenib was used as first line therapy and this was also used in all patients. Four patients needed to change to second-line treatment*:* 2 DTC patients (both used levantinib) and 2 MTC patients (1 used levantinib and 1 used sorafenib). The mean time usage of MKI was 21 months (P25-75 11-49).

The use of the full dose of MKI occurred in 20 patients (76.9%). The most common cause of non-use of the full dose is drug related side effects. All patients had adverse reactions, the most common reactions being skin reactions in 84% of patients followed by diarrhea in 44% (**Table 2**).

Of the twenty-six patients analyzed, 10 (38.5%) remain in use, 7 (26.9%) discontinued treatment due to disease progression, 5 (19.2%) suspended because of side effects, 2 (7.7%) died during treatment and 2 (7.7%) discontinued for other reasons.

Hypothyroidism treatment

Twenty-five patients were analyzed for dose escalation, one patient was excluded because he started treatment and immediately had to discontinue due to side effects.

From the patients analyzed, 23 (92%) needed to increase the levothyroxine dosage to achieve the target TSH (**Figure 1**). The mean dose before starting MKI was 1.98 ± 0.55 mcg/kg/day. After the initiation of MKI the maximal dose was 2.70 ± 0.75 mcg/kg/day. The median dose increase was 38% (P25-75 18-57) and occurred in the median time of 12 months (P25-75 8-20). Interestingly, the group of MTC patients had a more pronounced elevation in levothyroxine dose (1.96 ± 0.44 to 2.91 ± 0.82 mcg/kg/day; 47%) when compared to the group of patients with DTC (2.03 ± 0.67 to 2.36 ± 0.88 mcg/kg/day; 17%, P 0,028).

To explore if any characteristic was associated with a higher increase in levothyroxine dose we divided the patients in two groups: those with increase of less than 37% and those with increase of more than 38%. The group of patients with a more prominent elevation in levothyroxine dose was younger, had a longer use of MKI treatment and more sites with distant metastasis (**Table 3**).

DISCUSSION

The introduction of MKIs drugs improved the care of patients with advance thyroid cancer, since before the development of this class of drugs this group of patients had no therapy with impact on disease progression. Although, is important to notice that important related side effects are expected and they should be monitored and managed properly, as they directly impact life quality and treatment adherence. In addition to side effects, MKIs are associated with increased levels of TSH in prolonged treatments and induction of hypothyroidism, being often necessary to increase levothyroxine dosage and to regularly monitor thyroid function (CARHILL et al., 2013).

Here, we demonstrated that 23 of 25 patients using MKI (92%) patients needed to increase the levothyroxine dosage to achieve the target TSH and the median dose increase was 38% occurring in a median of 12 months . Interestingly, we observed that the need to increase levothyroxine dose was greater in MTC patients. This fact can be explained by the low target of TSH that DTC patients have to achieved and for that they could be used a higher dose since the beginning of the treatment.

Miyake et al. (2010) demonstrated that in 67.7% of patients with renal cell cancer using sorafenib, there were hypothyroidism development. Regarding the characteristics of the patients, the only factor that contributes to the patients developing loss of thyroid function was advanced age (MIYAKE et al., 2010). Several studies have also showed that hypothyroidism is a common adverse effect of vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy (VEGFR-TKI). The proposed mechanisms include capillary regression of thyroid tissue by blocking VEGFR and platelet-derived growth factor receptor (PDGFR), decreased thyroid hormone biosynthesis by inhibiting uptake of peroxidase and iodine, transmembrane transport of derived hormones thyroid disease, and increased type 3 deiodination (BAILEY et al., 2015).

Regarding this last possible mechanism, is important to notice that we observed that the group of patients who need to increase the levothyroxine dose over 38% had more sites with metastasis. Since we know that thyroid cancer metastasis could overexpress type 3 deiodinase (ROMITTI et al., 2012) this could be the mechanism of the hypothyroidism development. An analogue clinical situation will be the "consumptive hypothyroidism" that is related with tumors with high expression of the same enzyme (WEBERPASA et al., 2017).

Most patients using MKIs develop adverse events. In sorafenib treatment the most commonly reported adverse effects were hand foot syndrome, diarrhea, alopecia, rash, weight loss, and hypertension and in vandetanib treatment diarrhea, rash, nausea, and hypertension. In addition, rare adverse effects have been reported being: heart failure, thrombocytopenia and squamous cell carcinoma during therapy with sorafenib and squamous cell carcinoma and oophoritis with intestinal perforation during treatment with vandetanib (PITOIA et al., 2018). We also observed, as expected, that all patients developed side effects, which had to be managed for continued treatment.

In conclusion, we observed that the majority of thyroid cancer patients using MKI would need an increase in the levothyroxine dose of about 40%. Those patients with younger age, more time on MKI and with extensive disease are group in which these will be more critical. So especially in patients with these characteristics, we suggest that the monitoring for the need for levothyroxine replacement should be done with more caution.

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Table 1- Characteristics of patients

Age at diagnosis (years)	51.8 ± 17.5
Female – n (%)	14 (53.8)
Histology – n (%)	
Medullary	15 (57.7)
Papillary	9 (34.6)
Follicular	2 (7.7)
Lymph node metastases – n (%)	18 (69.2)
Number of distant metastases – n (%)	
1 site	3 (11.5)
2 sites	12 (46.2)
3 sites or more	11 (42.3)

*Data are expressed as the mean ± SD, median (*interquartile range P25-75 *) or frequencies*

Table 2- Adverse reactions to MKI treatment

Reaction Type – n (%)	
Skin	21 (80.7)
Diarrhea	11 (42.3)
Hypertension	3 (11.5)
Alopecia	4 (15.4)
Fatigue	3 (11.5)

Data are expressed as frequencies.

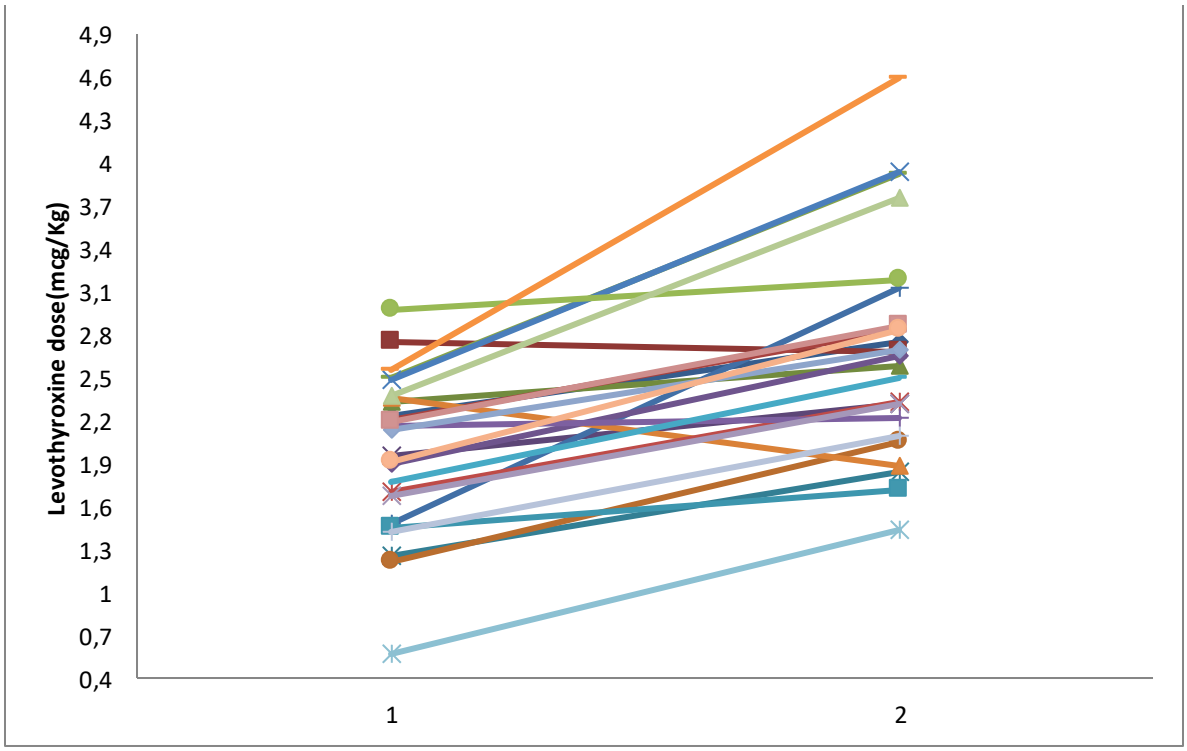
Table 3- Comparison of patients with high (38%) and low (<37%) levothyroxine dose increase

Characteristic n, %	**Increase < 37%**	**Increase > 38%**	**P**
Gender Female	7(58.3%)	6 (46.1%)	0.695
Age at diagnosis (years)	60.5 (13.0)	46.5 (16.8)	0.03
Time of MKI use (months)	12.6 (9.4-22.8)	49 (13.2-74)	0.015
Histology type MTC	5 (41.7%)	10 (77.0%)	0.111
DTC	7 (58.3%)	3 (23.0%)	
Lymp nodes' metastases	9 (75%)	8 (61.5%)	0.673
Distant Metastases sites			
1 site	0 (0%)	3 (23.1%)	0.047
2 sites	8 (66.7%)	3 (23.1%)	
3 sites or more	4 (33.3%)	7 (53.8%)	

Data are expressed: Median (Interquartile Range P25-75),

*Data are expressed as the mean ± SD, median (*interquartile range P25-75 *) or frequencies.*

Figure 1- Dose increase of levothyroxine per patient.



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5 CONSIDERAÇÕES FINAIS

No presente estudo foi possível observar que 92% dos pacientes com câncer de tireoide em uso de IMK precisou de um incremento na dose de levotiroxina de cerca de 40%, no tempo médio de uso de 12 meses.

Identificamos que nos pacientes com idade mais jovem, que utilizaram esses medicamentos por mais tempo e que possuem doença extensa (maior número de metástases) pertencem ao grupo em que a necessidade de aumento da dose de levotiroxina foi e mais crítica. Portanto, especialmente em pacientes com essas características, sugerimos que o monitoramento da necessidade de reposição de levotiroxina seja realizado com mais cautela e que o acompanhamento e monitoramento seja realizado com uma menor frequência de tempo.

Diversos estudos demostraram que o hipotireoidismo é um efeito adverso comum da terapia com IMK do receptor do fator de crescimento endotelial vascular (VEGFR-TKI). Os mecanismos propostos incluem regressão capilar do tecido tireoidiano, bloqueando o VEGFR e o receptor do fator de crescimento derivado de plaquetas (PDGFR), biossíntese reduzida do hormônio tireoidiano, inibindo a captação de peroxidase e iodo, transporte transmembrana de doenças tireoidianas dos hormônios derivados e aumento da desiodação do tipo 3.

Os IMKs são medicamentos com importantes efeitos colaterais relacionados, os quais devem ser acompanhados e corretamente manejados, pois impactam diretamente na qualidade de vida e aderência ao tratamento. No estudo foi possível observar a presença de efeitos colaterais em todos os pacientes analisados, sendo os principais efeitos: reações cutâneas, diarreia, hipertensão, queda de cabelo e fadiga.

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7 ANEXO

HOSPITAL DE CLÍNICAS DE PORTO ALEGRE

Grupo de Pesquisa e Pós Graduação

Carta de Aprovação

Projeto

2018/0399

Pesquisadores:

RAFAEL SELBACH SCHEFFEL

CARLA FERNANDA NAVA GRAZIELA CRISTINE GOERCK MARTA AMARO DA SILVEIRA DUVAL

Número de Participantes: 30

Título: Efeito dos inibidores multiquinase no metabolismo dos hormônios tireoideanos e necessidade de reposição hormonal em pacientes com câncer de tireoide

Este projeto foi APROVADO em seus aspectos éticos, metodológicos, logísticos e financeiros para ser realizado no Hospital de Clínicas de Porto Alegre.
Esta aprovação está baseada nos pareceres dos respectivos Comitês de Ética e do Serviço de Gestão em Pesquisa.

- Os pesquisadores vinculados ao projeto não participaram de qualquer etapa do processo de avalição de seus projetos.

- O pesquisador deverá apresentar relatórios semestrais de acompanhamento e relatório final ao Grupo de Pesquisa e Pós-Graduação (GPPG).

Assinado digitalmente por:
PATRICIA ASHTON PROLLA
Grupo de Pesquisa e Pós-graduação
27/08/2018 18:30:22

Impresso do sistema AGHU-Pesquisa por RAFAEL LEAL ZIMMER em 24/08/2018 14:37:11