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Sorafenib use in patients with radioiodine-refractory differentiated thyroid cancer – A five-year experience at the ISSSTE National Medical Center 20 de Noviembre in Mexico City

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Abstract

Background: *Sorafenib was the first oral multikinase inhibitor to be approved for the treatment of patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (DTC). The impact of this treatment is not known in the Mexican population.* **Method:** *A retrospective, observational study was carried out by reviewing 31 electronic medical records of conventional treatment-refractory patients with DTC who were treated with sorafenib within the period from January 2013 to January 2018.* **Results:** *A total of 31 patients met the inclusion criteria, with a higher frequency in women (71%), with a history of papillary DTC in 93.5%, histologic Grade I in 83.9%, and presence of vascular permeation in 67.7%. The majority of patients presented an Eastern Cooperative Oncology Group 1 at the onset of treatment (83.9%), and the most common site of metastasis was the lung in 64.5% of cases. The subjects had been previously treated with surgery (87.1%), radioiodine (74.2%), and radiotherapy (41.9%). Based on response criteria (lesion size reduction, basal thyroglobulin decrease, progression-free interval increase, tumor-associated symptoms decrease), stable disease was observed in 74.2% and an overall response rate of 25.8%. Mean progression-free survival (PFS) was 16.13 months, with a standard deviation of 2.15 months. Sorafenib was initiated at a dose of 800 mg/day, and in 30 patients (96.77%), the dose was reduced to 600 mg/day due to the presence of Grade 2 palmar-plantar erythrodysesthesia, with a mean reduction time of 11.6 weeks and, subsequently, 24 patients (80%) underwent a second dose reduction to 400 mg/day due to the presence of Grade 3 asthenia.* **Conclusions:** *Sorafenib increased PFS, lowered thyroglobulin levels, reduced tumor size, and decreased tumor-associated symptoms in patients with locally advanced or metastatic DTC who were refractory to standard treatment. In Mexican population, due to the toxicity that occurred in the patients, the dose reduction was performed in more than half of the patients.*

Key words: *Differentiated thyroid cancer. Sorafenib. Tyrosine kinase inhibitors. Iodine-refractory cancer.*

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Uso de sorafenib en pacientes con cáncer de tiroides diferenciado refractario al yodo: una experiencia de cinco años en el ISSSTE Centro Médico Nacional 20 de Noviembre en la Ciudad de México

Resumen

Antecedentes: *El sorafenib fue el primer inhibidor oral de cinasas múltiples aprobado para el tratamiento de pacientes con cáncer de tiroides diferenciado (DTC) localmente avanzado o metastásico refractario al yodo radioactivo. El impacto de este tratamiento no se conoce en la población mexicana.* **Método:** *Se realizó un estudio observacional retrospectivo mediante la revisión de 31 registros médicos electrónicos de pacientes con tratamiento refractario convencional con DTC que fueron tratados con sorafenib en el periodo comprendido entre enero de 2013 y enero de 2018.* **Resultados:** *Un total de 31 pacientes cumplieron los criterios de inclusión, con mayor frecuencia de mujeres (71%), con antecedentes de DTC papilar en un 93.5%, grado histológico I en el 83.9% y presencia de permeabilidad vascular en el 67.7%. La mayoría de los pacientes presentaron una puntuación ECOG 1 al comienzo del tratamiento (83.9%) y el sitio más común de metástasis fue el pulmón (en el 64.5% de los casos). Los sujetos habían sido tratados previamente con cirugía (87.1%), radioyodo (74.2%) y radioterapia (41.9%). Según los criterios de respuesta (reducción del tamaño de la lesión, disminución de la tiroglobulina basal, aumento del intervalo libre de progresión, disminución de los síntomas asociados con el tumor), se observó una enfermedad estable en el 74.2% y una tasa del 25.8% de respuesta general. La supervivencia libre de progresión (SLP) media fue de 16.13 meses, con una desviación estándar de 2.15 meses. El sorafenib se inició con una dosis de 800 mg/día, y en 30 pacientes (96.77%) la dosis se redujo a 600 mg/día debido a la presencia de eritrodisestesia plantar de palmera grado 2, con un tiempo de reducción promedio de 11.6 semanas; posteriormente 24 pacientes (80%) se sometieron a una segunda reducción de dosis a 400 mg/día debido a la presencia de astenia de grado 3.* **Conclusiones:** *El sorafenib aumentó la SLP, disminuyó los niveles de tiroglobulina, redujo el tamaño del tumor y disminuyó los síntomas asociados con el tumor en pacientes con DTC localmente avanzado o metastásico que eran refractarios al tratamiento estándar. En la población mexicana, debido a la toxicidad que se produjo en los pacientes, la reducción de la dosis se realizó en más de la mitad de los pacientes.*

Palabras clave: *Cáncer diferenciado de tiroides. Inhibidores de la tirosina cinasa. Sorafenib. Cáncer refractario al yodo.*

Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine neoplasm, with this malignancy occupying the fifth place in women in the United States[1,2]. Clinical evolution can range from an indolent tumor with low mortality to an aggressive disease. The most common lineages are papillary and follicular carcinoma, which account for more than 90% of cases[1,2].

The established treatment has yielded excellent results with the use of surgery, radioiodine, and thyroid-stimulating hormone (TSH) suppression, with a 5-year relative survival of 98%[3,4].

However, around 5% of patients with DTC present with locally advanced disease and 10% develop distant metastasis, which is the main cause of mortality in thyroid cancer[1,2].

There are factors associated with unfavorable prognosis. The American Thyroid Association guidelines classify DTC with gross extrathyroid extension, distant metastasis, incomplete tumor resection, post-surgical increased thyroglobulin levels, compromised nodules larger than 3 cm, and follicular cancer with extensive vascular invasion as high-risk factors for recurrence and radioiodine refractoriness, which makes for more than standard therapy to be required for treatment[4]. Understanding the biological behavior of DTC has led us to explore the use of different therapies against the molecular targets.

DTC has been associated with different genetic mutations, which generally involve the mitogen-activated protein kinase (MAPK) pathway, the mammalian target of rapamycin, and vascular endothelial growth factor (VEGF) mutations. DTC oncogenesis occurs through the MAPK signaling pathway. The most common genetic mutation is *BRAF V600E*, which is present in 60% of well-differentiated papillary carcinomas. Other genes involved such as *KEAP1, NQO1,* and *NQO2* have been described recently to be involved in poorly differentiated thyroid carcinoma and extrathyroid metastases. Angiogenesis is essential for tumor cell growth, maturation, and metastatic expansion. Therefore, VEGF expression

is associated with an elevated risk for recurrence and a decrease in the disease-free interval[5-8]. Knowledge of the MAKP pathway and VEGF receptors has led to the use of molecular therapies such as tyrosine kinase inhibitors (TKIs), which inhibit multiple signaling pathways not only MAPK but also their greatest advantage is the oral administration[9-12].

The two drugs that have been approved by the FDA for iodine-refractory DTC are Lenvatinib and sorafenib, based on the multicenter, randomized, double-blind, placebo-controlled Phase III DECISION and SELECT trials, respectively, which demonstrated a progression-free interval benefit versus placebo. Sorafenib inhibits BRAF, VEGFR1'3, RET, Raf-1, and PDGFRb. It was approved for use in radioiodine-refractory DTC in 2013. The present analysis was carried out to assess sorafenib efficacy and safety in Mexican patients with locally advanced or metastatic disease who had disease progression with the standard treatment[13-15].

Materials and methods

A retrospective, observational study was carried out searching the ISSSTE National Medical Center "20 de November" electronic database for DTC diagnosed patients treated within the period from January 2013 to January 2018 who met the following inclusion criteria: age older than 18 years; DTC histopathologic confirmation; the Eastern Cooperative Oncology Group (ECOG) 0-2 performance status; previous treatment with surgery, radiotherapy, radioiodine, or no possibility of any other treatment with curative purposes; sorafenib-based initial treatment in this setting; and no previous treatment with any TKI. Among the exclusion criteria, patients with other histologic variants such as anaplastic thyroid carcinoma and patients who did not complete 1 month of treatment with sorafenib for any reason were eliminated. A central tendency analysis was carried out with the SPSS version 26 program.

Results

Out of 37 identified electronic medical records, 31 DTC diagnosed patients (6 failed to meet the inclusion criteria) who started treatment with sorafenib within a 5-year period were assessed. Table 1 summarizes the demographic characteristics. The most common initial symptom at diagnosis was a palpable mass in the neck (80.6%), followed by dysphonia (6.5%), dyspnea, odynophagia, dysphagia, and lower limb paresthesia, with 3.2% each.

Table 1. Demographic characteristics (n = 31)

Variable	Frequency
Gender	
Female	22 (71%)
Metastasis	
Pulmonary	20 (64.51%)
Locoregional	11 (35.48%)
Bone	5 (16.12%)
Mediastinal	3 (9.67%)
One single site	19 (61.30%)
Two or more sites	12 (38.70%)
ECOG	
1	26 (83.90%)
2	5 (16.10%)
Lineage	
Papillary, Grade 1	24 (77.40%)
Papillary, Grade 2	5 (16.10%)
Follicular, Grade 1	2 (6.50%)
Previous treatment	
Surgery	27 (87.10%)
Total radioiodine	74.20%
RAI median cumulative dosew	423.54 mCi
RAI cumulative dose min.	100 mCi
RAI cumulative dose max.	1400 mCi
External conformational radiotherapy	13 (41.90%) 60 Gy in 33 fractions

ECOG: Eastern Cooperative Oncology Group.

Clinical stage was assessed with the American Joint Committee on Cancer tumor-node-metastasis (TNM) 7th edition classification, with the most common stage among the patients being clinical Stage II (74.1%) followed by Stage III (19.3%) and, finally, Stage IVB with 6.6%. A total of 87.1% of patients with DTC were initially treated with surgery, 74.2% received radioiodine (with a median cumulative dose of 423.54 mCi), and 41.9% received radiotherapy sometime during the treatment of recurrence or during primary treatment as adjuvant (Table 1).

The scale used to measure the performance status was ECOG. Most patients were ECOG 1 (83.9%) and ECOG 2 (16.1%) (Table 1).

The most common site with metastasis at the beginning of treatment was the lung in 64.5%, followed by locoregional in 35.4%, bone in 16.1%, and mediastinal in 9.6%, with involvement of a single region being more common, with 61.3% of cases, and 38.7% with two or more affected regions.

Stable disease was shown by 74.2% of patients, with partial response (more than 30% disease reduction as evaluated by RECIST) observed in 25.8%; median progression-free survival (PFS) was 16.13 months, with a

Table 2. Toxicity observed in the sample

Toxicity	All grades (%)	Grade 3 (%)
Asthenia	25 (80.60)	11 (36)
Hand-foot syndrome	20 (64.50)	20 (65)
Diarrhea	15 (48.30)	6 (20)
Mucositis	15 (48.30)	6 (20)
AHT	8 (25.80)	19 (62.50)
Rash	6 (19.30)	2 (5.20)
Pain	3 (9.60)	0
Hemorrhage	3 (9.60)	0
Alopecia	2 (6.40)	0
Weight loss	2 (6.40)	0
Pruritus	2 (6.40)	0
Nausea	2 (6.40)	0
Anorexia	1 (3.20)	0
Cough	1 (3.20)	0
Dyspnea	1 (3.20)	0
Thrombocytopenia	1 (3.20)	0

standard deviation of 2.15 months, minimum of 5 months and maximum 45 months. More than 50% of the population is still alive and, for this reason, calculating an overall survival estimate was not possible at the moment of this analysis.

The systemic treatment started at the moment of disease recurrence or progression with sorafenib 800 mg/day recommended dose.

With regard to treatment tolerance, the most commonly observed toxicity was asthenia (80.6%), followed by hand-foot syndrome or palmar-plantar erythrodysesthesia (64.5%), diarrhea and mucositis (48.3%), systemic arterial hypertension (25.8%), rash (19.3%), pain and hemorrhage (9.6%), alopecia, pruritus, nausea and weight loss (6.4%), and anorexia, cough, dyspnea, and thrombocytopenia (3.2%) (Table 2).

Sorafenib dose reduction to 600 mg/day was required in 96.77% of patients, with the most common cause being G3 palmar-plantar erythrodysesthesia (43.3%), with a mean reduction time at 11.6 weeks, and with a minimum of 2 weeks and a maximum of 192.8 weeks. The second sorafenib reduction to 400 mg/day (which is considered the second level of treatment reduction) was carried out in 80% of patients, with the main cause being G2 or G3 asthenia (45.8%).

Discussion

The use of sorafenib in patients with locally advanced or metastatic DTC who have been previously treated and have no possibility of any treatment with curative intent was established with the results of the DECISION trial, where an overall response and PFS benefit were demonstrated; after approval by each country's regulatory authorities, the use of sorafenib was initiated. Since there is no available information in Mexico on clinical evolution and tolerance to the drug, we undertook this study of patients who received sorafenib and met the previously described inclusion criteria. Most part of the population (69%) were female, which is expected. Median age at diagnosis was 57.3 years, and the most common histologic type was papillary carcinoma. In spite of a favorable prognosis with a high rate of cure at 10 years, there is a group of patients with less indolent disease that progresses or recurs with the employed treatments. Among the analyzed population, more than 70% had received surgery as initial treatment in addition to hormone suppression with levothyroxine and, in some cases, radioiodine was used and even radiotherapy in those patients with high-risk factors for recurrence. However, there are data related to this non-indolent evolution, such as vascular permeation (associated with FTC), which were present in 67.7% of cases, as well as the TNM-based stage the patients were at. According to this classification, no patient diagnosed with clinical Stage I treated with surgery, radioiodine, and TSH suppression was observed to have this evolution; most patients (74.1%) were at clinical Stage II and had high-risk factors for recurrence. It should be noted that there is a percentage of patients (6.6%) who are initially diagnosed at locally advanced stages where the possibility of initial surgical treatment and radioiodine is not feasible due to the heavy tumor burden they have at diagnosis. Unfortunately, in Mexico, there is still population wrongly diagnosed which results in delay of opportune treatment. The most common signs or symptoms at diagnosis were a palpable mass in the neck in 80.6% of subjects, although there were patients with dyspnea or dysphagia, which are related to highly extended disease at diagnosis.

The population of patients who started treatment with sorafenib was assessed with the ECOG scale, and only patients with ECOG 0-2 were included in the study. In most cases, the patients were in good clinical conditions, with minimal symptoms and ECOG 1 being shown by 83.9% of patients; no patients were found

with an ECOG of 0, and there was a low percentage of ECOG 2 subjects.

The efficacy results are positive in our sample in terms of responses; since this is a smaller sample in comparison with the DECISION trial population, this makes a jumpstart for a bigger study for statistical reproducibility in the future. In our analysis, median PFS was 16.13 months; in the DECISION trial, a median PFS of 10.8 months was reported for the patients who received sorafenib. As for overall responses, partial responses were observed in 25.8% of cases, with no complete responses being found. The highest benefit that has been observed with the use of sorafenib is in terms of disease stabilization. Stable disease was present in 74.2% of patients, whereas in the approval study, stable disease was reported in 74%. Finally, all treated patients responded by showing a decrease in the levels of thyroglobulin and we can say that clinical benefit was of 100% (the clinical benefit is the result of the global response plus the stable disease, none of the patients presented immediate progression of the disease from at the moment of sorafenib initiation to the time of the end of the study). In terms of efficacy, the results are similar to those of the DECISION trial. As for the best treatment sequence, it remains unknown. The SELECT (Lenvatinib) study included 25.3% of patients who had previously received sorafenib, and the PFS found in this group was 15.1 months in comparison with placebo. In the analyzed population, only 25.8% received a second line of treatment, 22.6% received sunitinib, and one patient received pembrolizumab within the setting of a clinical trial followed by the third-line Lenvatinib. Decision and SELECT were the approval studies of TKI for DTC, but real data of TKIs in the real world are limited. These drugs are used according to the clinical features of each patient, which is different from the clinical trials. In the real practice, we can adjust the dosage of TKIs according to adverse events and interrupting the dose for short periods (2 weeks) and reinstalling the drug with a lower dose. Kim et al. made a study in 2018, were the use of sorafenib, and are described in the real world in Korea. In this study 71 medical records, 23 treated with Lenvatinib and 48 with sorafenib were reviewed. The most common histological types were papillary thyroid cancer (69%) and follicular (22.5%) and poorly differentiated (8.6%). In our study, the poor differentiated population was not included, although the papillary population was 93.5% in our study. Initial sorafenib dose in Korean study and our study was 800 mg daily. The most common metastatic lesion site was the lung (78.3%) which in our study was of 64.5% very similar to Korean population. The dose reduction in Korean trial was made in 56.3% due to adverse effect and the most frequent toxicity was hand-foot skin reaction in 87.5%, diarrhea 62.5%, and anorexia 60.4% which compared to our study is similar in the hand-foot skin reaction (64.5%) and diarrhea in 48.3%. In both studies, no new toxicities were found due to sorafenib use than those already established. Most of the adverse effects were solved by dose reduction and medical therapy[16]. In another study also made in Korea involving the use of sorafenib and Lenvatinib in real world, patients were a multicenter retrospective cohort study with a population of 98 patients radioiodine refractory with DTC. The primary objective of the study was to evaluate the overall survival and their result of median overall survival was 41.5 months for sorafenib and the median for PFS was 13.5 months (in our study was 16.18). In this study, 32 patients treated with sorafenib had disease progression had a second-line treatment with Lenvatinib. Treatment interruption was made in 19% of patients, reduction dose in 53%, and drug suspension in 21%. Compared to our study, where most patients underwent dose reduction and only one had total drug suspension[17].

Treatment with sorafenib was at the 800 mg/day recommended dose, which is the dose the patients were started at. The most common adverse event, at all grades, was asthenia in 80.6%, followed by hand-foot syndrome in 64.5%, diarrhea and mucositis in 43.3%, and systemic arterial hypertension in 25.8%, among the most common; unlike other studies, the percentage of asthenia was higher in our population. The first sorafenib dose reduction to 600 mg/day was applied in 97.7% of patients at 11.6 weeks, with a minimum of 2 weeks and a maximum of 192.8 weeks. The second sorafenib dose reduction to 400 mg/day was carried out in 80% of patients. The most common cause for the first-dose reduction was Grade 3 hand-foot syndrome (43.3%). According to the suggested dose adjustment guidelines, any Grade 3 toxicity warrants treatment interruption and, on recovery, one dose level reduction. The second most common cause for sorafenib dose reduction was G2 and G3 asthenia in 45.8% of patients. Patients suspended sorafenib for 2 weeks and the initiated at a lower dose for both reduction times. According to findings reported in the DECISION trial, the most common cause of toxicity and treatment reduction and interruption was hand-foot syndrome, which occurred in 66.2% of patients, whereas in our analysis, it occurred in 97.6% of subjects. We do not know why there appears to be lower tolerance to the sorafenib 800 mg standard dose; it is possible that the studies contemplate Anglo-Saxon

or European populations, and the fixed dose is established in a population with height and weight that are different to those in our country.

All patients showed reductions in the levels of thyroglobulin, with its increase being evident at disease progression.

The importance of the study is to add new information about sorafenib's side effects and tolerance in Mexican population. Although this study has limitations due to its retrospective design, the clinical experience outside the clinical trials are still not entirely known.

Most of our patients who have disease progression have no access to Lenvatinib, and therefore, another TKI is used although the results are not as those expected with Lenvatinib. Other limitations are we do not have the histological subtypes due to failure for extended pathological studies made in this institution, in routine reports, they only specify the type due to the massive quantity of patients that undergo pathology diagnosis. Although in the studies previously mentioned, the most common histological types reported were papillary thyroid cancer.

Despite this limitation, our study is the first of its kind to report adverse events in Mexican population as well as the clinical benefit of sorafenib use in this population. We recommend in the future with a larger population to study with a longer period of time for reproducibility and follow-up of this study.

Conclusions

Sorafenib outcomes in the Mexican population proved to be beneficial in the progression free survival, the side effects where similar to those reported in the international trials and the dose adjustment according to toxicity done at the right timing results in therapeutic attachment, avoiding serious side effects and treatment delay.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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