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ORIGINAL ARTICLE

The experience of an Endocrinology Division on the use of tyrosine multikinase inhibitor therapy in patients with radioiodine-resistant differentiated thyroid cancer

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Abstract

Purpose To describe the experience of our Division of Endocrinology with multikinase inhibitor (MKI) treatment in radioiodine-resistant differentiated thyroid cancer (DTC) patients.

Methods Adults patients with a diagnosis of DTC treated with an MKI drug from March 2011 to October 2018 were registered into a retrospective database. Primary objectives were: the assessment of progression-free survival (PFS) and radiographic response evaluated according to RECIST v. 1.1. Adverse events (AEs) were evaluated by using Common Terminology Criteria for Adverse Events v. 5.0.

Results Twenty-two patients were treated with MKIs (21 with sorafenib, one with lenvatinib as first-line treatment). Seven patients required a second-line therapy with lenvatinib and one patient required a third-line treatment with pazopanib. Median duration of treatment was 11.2 (4.8–79.6) months. Best responses with sorafenib were partial response (PR) in two patients (11%), stable disease (SD) >6 months in 13 patients (72%), and progressive disease (PD) in three patients (17%). Best responses with second-line lenvatinib were PR in one patient (33%) and SD in two patients (66%). Median PFS was 31.5 months. AEs were present in 19 (90%) patients under sorafenib. The most common AEs were hand–foot syndrome (HFS) (67%), diarrhea (52%), and hypertension (52%). Definitive withdrawal was necessary in only one patient (4.7%).

Conclusions Our study reflects the real-world clinical experience of an Endocrinology Division on the management of radioiodine-resistant DTC patients with sorafenib and lenvatinib, showing a beneficial therapeutic effect with acceptable tolerability.

Keywords Multikinase inhibitor therapy · Sorafenib · Lenvatinib · Differentiated thyroid cancer · Radioactive iodine refractory

Introduction

Nearly 10–20% of patients with differentiated thyroid cancer (DTC) will develop distant metastases. At least half of them will not respond to radioactive iodine (RAI) [1]. In this subgroup of patients, the 10-year overall survival (OS) drops to 10% and the mean life expectancy is 3–5 years [1]. Conventional chemotherapy has limited efficacy with marked toxicity [2]. The advent of multikinase inhibitor (MKI) therapy has led to a radical change in the treatment of RAI-refractory patients. Sorafenib and lenvatinib have been approved in these cases by several drug regulatory agencies around the world including the Food and Drug Administration and the European Medicines Agency. Both drugs have demonstrated to increase the progression-free survival (PFS) when compared to placebo in phase III clinical trials [3, 4]. No OS benefit has been demonstrated yet. This was probably related to the crossover that occurred in most patients who progressed on placebo treatment to the open arm [3, 4]. Additional vascular endothelial growth factor receptors (VEGFR)-directed kinase inhibitors including axitinib, pazopanib, cabozantinib, and sunitinib have also activity in metastatic DTC based upon phase II trials [5–8].

The 2015 American Thyroid Association guidelines state that MKI therapy should be considered for the treatment of

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RAI-refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease, not otherwise amenable to local control by other approaches [9]. However, the optimal timing for the start of MKI therapy remains unclear and a multicenter, international clinical trial is trying to elucidate this topic [10]. Additionally, MKIs usually produce a number of adverse events (AEs) [3, 4]. Although most of them will be manageable, nearly 50% will be serious AEs that could negatively impact on the quality of life of these patients, making the time to start of MKI therapy a challenge scenario in actual clinical practice.

This paper describes the experience of our Division of Endocrinology with MKI treatment in DTC patients gained during the last 8 years. The primary objective was to determine response and PFS in this group of patients. Secondary objectives included describing the toxicities and tolerability of these drugs and the mean time of AEs occurrence during MKI therapy.

Patients and methods

Study population and data collection

Adults patients (≥18 years old) with a diagnosis of DTC treated with an MKI drug from March 2011 to October 2018 were registered into a retrospective database. All patients had a baseline and at least one follow-up imaging study to assess response after 3–6 months of MKI therapy. Patients with medullary and anaplastic thyroid carcinoma were excluded. All patients had RAI-refractory disease, defined as RAI non-avid lesions, progressive lesions despite RAI avidity during treatment, and/or cumulative RAI activity >600 mCi [11].

Radiographic assessments and definitions

Computed tomography (CT) scans of the neck, thorax, and/or abdomen, depending on the localization of the metastatic lesions, were used to determine disease stability or disease progression before and after the treatment with MKI drugs. RECIST (version 1.1) was used to determine responses. We described the presence of partial response (PR), stable disease (SD), or progressive disease (PD) at 3, 6, 12, 18, and then every 6 months after the initiation of treatment with MKIs. Tumor response was classified as PR when the sum of the diameters of target lesions decreased by ≥30%, SD when the change was between 19% and 29%, and as PD when an increase of ≥20% in the sum of the diameters of the target lesions was observed [12].

AEs were evaluated by using Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0 [13].

Statistical analysis

Quantitative data were described as means (standard deviation), while qualitative data were expressed in percentages. We defined PFS as the time from MKI therapy initiation until disease progression or death. OS was defined as the percentage of patients who were alive after they had been treated with MKI therapy. PFS and OS were estimated using the Kaplan–Meier curve. Statistical analysis was performed using SPSS software (v.22).

Results

Clinical characteristics

From March 2011 to October 2018, 22 patients initiated therapy with MKI, 21 of them were treated with sorafenib while one was treated with lenvatinib as first-line treatment. Seven patients that were under sorafenib treatment required a second-line therapy with lenvatinib and only one patient required a third-line treatment with pazopanib. The baseline characteristics of these patients are detailed in Table 1.

One patient who received sorafenib during 40 months prescribed outside our Division was excluded because she did not have distant metastatic disease either progressive or symptomatic before the MKI initiation and sorafenib was withdrawn when she first attended our hospital.

To evaluate the response to treatment and the PFS, three patients under sorafenib treatment and one patient under lenvatinib treatment were excluded because they had less than 3 months of therapy and as they did not have image studies yet, we were unable to assess the tumor response. These four patients were under MKI therapy at the time of the data cutoff for the analysis and they had no clinical evidence of disease progression. To describe the MKIs AEs profile, these four patients were included in the analysis.

In the majority (68%) of our patients, MKI treatment was prescribed due to PD (between 6 and 12 months). Slow PD was shown in two cases (24 and 48 months prior to MKI initiation). Both patients had pulmonary lesions that had reached 1 cm and were close to the hilum in one case and in subpleural location in the other case. In five patients, MKI therapy was started due to rapidly progressive disease and large tumor burden, including one patient with local unresectable thyroid cancer at diagnosis who received sorafenib after local external beam radiation therapy.

Radiographic responses and PFS

The median duration of treatment was 11.2 (4.8–79.6) months. Out of 18 patients that received sorafenib for >3 months, only two (11%) patients achieved PR at

Table 1 Patient's characteristics

Age at diagnosis (years)	
Median (range)	55 (29–72)
Age at MKI therapy initiation (years)	
Median (range)	61 (36–75)
Sex	
Female/Male	12/10
ECOG PS	
0	12 (54%)
1	10 (46%)
Histology	
Papillary	14 (64%)
Follicular	6 (27%)
Hürthle	2 (9%)
Target lesions	
Neck and mediastinum	14 (63%)
Lung	14 (63%)
Bone	8 (36%)
Others	2 (9%)
Cumulative radioiodine activity (mCi)	
Mean (standard deviation)	487 ± 390

MKI multikinase inhibitor, *ECOG PS* Eastern Cooperative Oncology Group Performance Status

12 months and 13 (72%) patients had SD >6 months as the best response to treatment. Three patients (17%) had PD in the first 5 months after sorafenib initiation (Table 2). At the time of the data cutoff for the analysis, seven patients maintained SD with sorafenib and 11 patients had PD. Out of the 11 patients that had PD after sorafenib as first-line treatment, seven received lenvatinib as second-line treatment: one of them achieved a PR at 6 months of treatment, two patients had SD, and four had <3 months of therapy, including one patient in whom lenvatinib was interrupted due to the presence of recurrent severe proteinuria after 1 month of treatment. He had SD for 11 months under a third-line MKI treatment (pazopanib 400 mg/day). The other three patients who had <3 months of therapy with lenvatinib were receiving the drug at the time of the data cutoff, without clinical evidence of disease progression. Considering the entire cohort at final follow-up, PR rate was 5.5%, SD 55.5%, and PD 39% (Table 2).

One additional patient initiated lenvatinib as first-line treatment but had <3 months of treatment and the response to treatment could not be assessed.

Median PFS was 31.5 months (Fig. 1a). OS had not reached its median value at the time of analysis, but at 14 months it was 68% (Fig. 1b). Considering first-line therapy only, median PFS dropped to 16.5 months (Fig. 1c).

Adverse events

Out of 21 patients under sorafenib therapy (median duration treatment of 9.1 months), 19 (90%) had at least one AE.

The most common AEs with sorafenib can be seen in Table 3. The majority of the AEs occurred during the first 3 months after the initiation of the MKI therapy (Fig. 2). Serious (grade 3 or 4) AEs occurred in nine (43%) patients receiving sorafenib (Table 3). Hand–foot syndrome and fatigue were the most common serious AEs in our cohort. One patient developed grade 3 thrombocytopenia 4 months after sorafenib initiation and this AE disappeared after a dose reduction of sorafenib (from 800 mg/day to 400 mg/day). Secondary malignancy was seen in one patient who developed squamous cell carcinomas (SCCs) of the skin after sorafenib treatment (initially on his back and 23 months later, two SCCs in the forearm and one in the ear). All of them were surgically removed and no other suspicious lesion was detected at 56 months of follow-up under MKI therapy.

All patients were prescribed sorafenib 400 mg by mouth twice a day as a starting dose. However, 13 patients (62%) required dose reductions and nine patients (43%) required temporary withdrawals. Definitive withdrawal was necessary in only one patient due to heart failure, which occurred after 9 months of treatment. In this patient, the initial ejection fraction before sorafenib prescription was 67%, which decreased to 25% when heart failure developed. One month after sorafenib withdrawal, the ejection fraction increased to 55% after additional cardiovascular medications. She died 5 months later after sorafenib withdrawal from sudden death. Four other patients died due to disease progression and occurred at 5, 5, 12, and 12 months after the start of sorafenib treatment, respectively.

Common AEs in the eight patients who received lenvatinib (median treatment duration of 2 months) are detailed in Table 4. Six patients started with full dosage (24 mg/day). One patient started with 20 mg because it was the initial dose provided by her health insurance company and in other patient, the starting dose of lenvatinib was 10 mg due to the development of heart failure after previous sorafenib therapy. Three patients (37%) required dose reductions and temporary withdrawals and only one patient (12%) had to interrupt lenvatinib due to severe recurrent proteinuria after 1 month of MKI initiation. No secondary malignancies were detected in patients receiving lenvatinib. No death occurred in our cohort during lenvatinib treatment.

Discussion

MKIs have shown to improve PFS in patients with structurally progressive, RAI-refractory DTC [3, 4]. In the

Table 2 Evolution of radiographic responses during multikinase inhibitor therapy

Patient	First-line sorafenib			Second-line lenvatinib		Comments
	Best response	Final response	Duration of treatment (months)	Best response	Duration of treatment	
1	PR	PD	30	Not assessed	1	
2	PR	PD	79	Not assessed	1	
3	SD > 6 months	PD	10	PR	18	
4	SD > 6 months	PD	21.3	SD	3	
5	SD > 6 months	PD	18	SD	3.8	
6	SD > 6 months	PD	16	Stopped due to AE	1	SD under pazopanib 11 months
7	SD > 6 months	SD	6	–	–	
8	SD > 6 months	SD	15	–	–	
9	SD > 6 months	SD	9	–	–	
10	SD > 6 months	SD	6	–	–	
11	SD > 6 months	SD	6	–	–	
12	SD > 6 months	SD	6	–	–	
13	SD > 6 months	SD	9	–	–	Died (sudden death)
14	SD > 6 months	PD	12	–	–	Died[a]
15	SD > 6 months	PD	12	–	–	Died[a]
16	PD	PD	4	Not assessed	2	
17	PD	PD	5	–	–	Died[a]
18	PD	PD	5	–	–	Died[a]

PR partial response, *SD* stable disease, *PD* progressive disease, *AE* adverse event

[a]Disease-related death

DECISION trial, sorafenib showed a mean PFS of 10.8 months compared to 5.8 months with placebo [3]. Outside clinical trials, mean PFS in patients receiving sorafenib was reported between 7.2 and 19 months [14–17], which is similar to what we showed in our study considering first-line therapy with sorafenib (16.5 months). The majority of patients receiving sorafenib achieve SD as best response with SD ≥6 months between 41.8% and 67% of cases and PR rates between 12% and 20% [3, 14–16]. In our cohort, 72% of the patients had SD ≥6 months and two patients (11%) demonstrated PR.

Lenvatinib was approved in February 2015 by the FDA based on the results of the SELECT trial, which reported a PFS of 18.3 months compared to 3.6 months with placebo [4]. Since it was not approved up to May 2018 in our country, lenvatinib was mainly used as a second-line therapy in our cohort. The subgroup of patients that received a second-line therapy with lenvatinib included seven patients that had PR under sorafenib. This illustrates that 50% or less of RAI-refractory patients usually receive a second-line MKI therapy [18]. Salvage therapy with lenvatinib after sorafenib failure has been proved to be beneficial [4, 17], although PFS is lower in comparison to when used in MKI-naïve patients (18.7 vs. 15.1 months) [4]. Due to the lack of head-to-head comparison studies, whether lenvatinib or sorafenib should be the first option for first-line treatment of RAI-refractory DTC patients is still uncertain. In our study, PR was seen in one patient (33%) and SD in two patients (67%) under second-line therapy with lenvatinib. However, the median duration of treatment under lenvatinib was only 2 months.

Considering all line treatments, median PFS of our group of patients was 31.5 months. Molina-Vega et al., in a cohort similar to ours (17 included patients: 16 treated with sorafenib and one treated with lenvatinib as first-line treatment, and four patients treated with lenvatinib and three patients treated with axitinib as second-line treatment), showed a median PFS of 18 months, PR was 35.3% and SD ≥6 months was 58.8% [15].

One patient with unresectable DTC received sorafenib after external beam radiation therapy. He did not suffer from any local side effects. Some data suggest that lenvatinib or pazopanib could be useful as neoadjuvant therapy in DTC patients [19]. Danilovic et al. recently described the use of sorafenib preoperatively for tumor reduction, allowing surgery [20]. Our patient had a cervical mass, pulmonary and bone metastasis as target lesions, and he had SD after 9 months of sorafenib treatment.

AEs were present in 90% of patients receiving sorafenib, and in 43% of cases it was grade 3 or 4. This was similar to

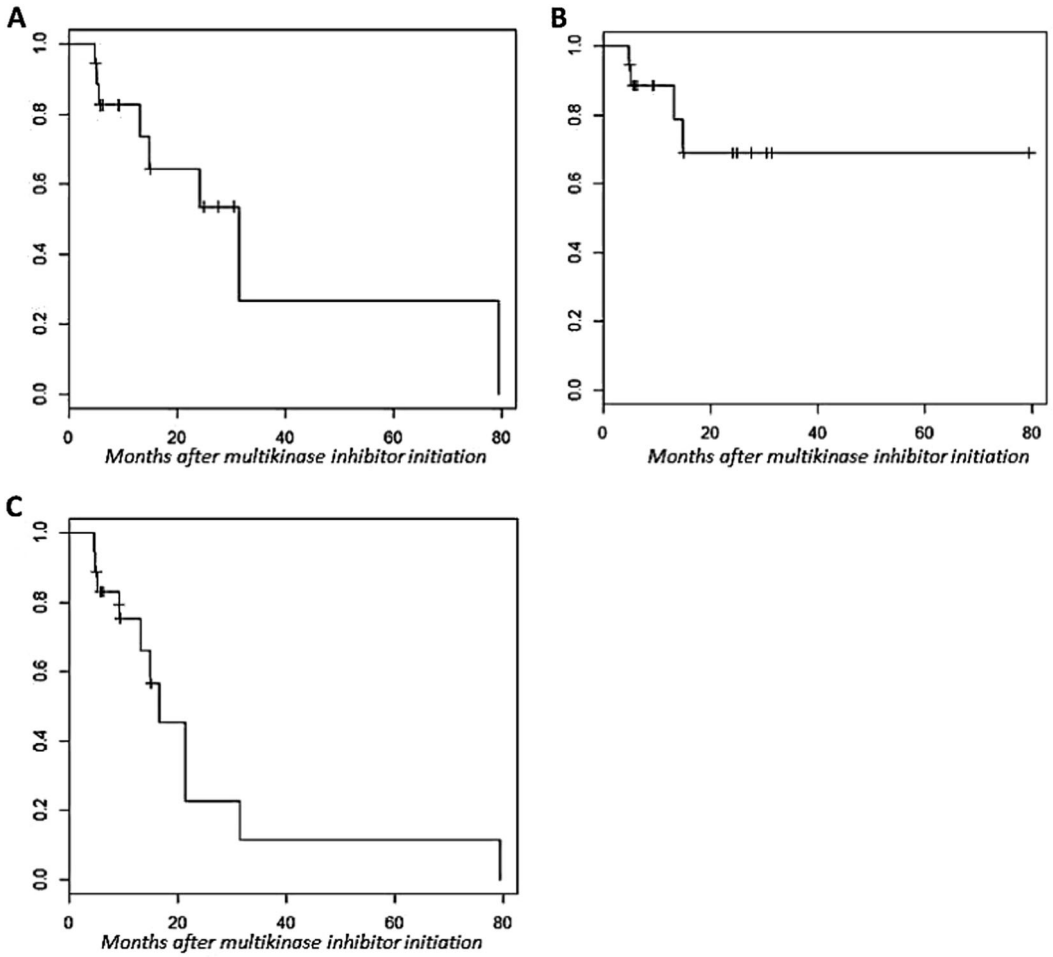

Fig. 1 Kaplan–Meier analysis of progression-free survival (**a**) and overall survival (**b**). **c** Progression-free survival curve considering first-line treatment only

Table 3 Common adverse events with sorafenib treatment

	All grades	Grade 3 or 4	Median time[a]
Any AE	19 (90%)	9 (43%)	3
Hand–foot skin reaction	14 (67%)	3 (14%)	3
Diarrhea	11 (52%)	2 (9%)	4
Hypertension	11 (52%)	2 (9%)	1
Fatigue	9 (43%)	3 (14%)	1
Weight loss	8 (38%)	0	5
Anorexia	6 (29%)	1 (5%)	1
TSH increase	3 (14%)	0	1
Alopecia	3 (14%)	0	2
Hepatotoxicity	2 (9%)	1 (5%)	4.5
Cytopenia	2 (9%)	1 (5%)	3.5
Ejection fraction decreased	2 (9%)	1 (5%)	5.5

[a]Median time after the initiation of the multikinase inhibitor for developing the adverse event

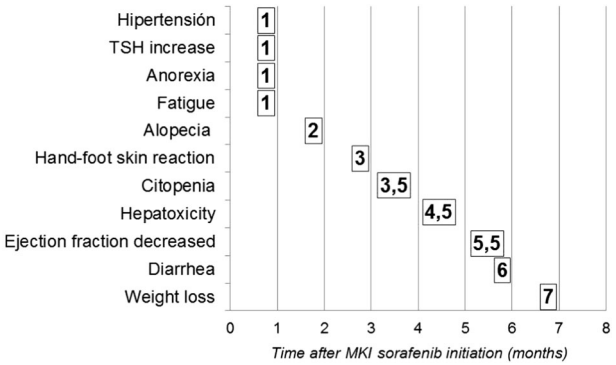

Fig. 2 Median time for adverse-event development after multikinase inhibitor initiation (months)

what was reported in the DECISION trial (98.6% and 37.2%, respectively) [3]. Hand–foot skin reaction, diarrhea, and hypertension were the most common AEs observed in our patients treated with sorafenib, in agreement with other published studies [3, 14, 15]. Although the majority of AEs

Table 4 Common adverse events under lenvatinib

	All grades	Grade 3 or 4	Median time[a]
Any AE	5 (62%)	5 (62%)	1
Hypertension	4 (50%)	2 (25%)	1
Hand–foot skin reaction	3 (37%)	2 (25%)	2
Proteinuria	3 (37%)	2 (25%)	1
Diarrhea	3 (37%)	0	1
Fatigue	2 (25%)	0	1
Cytopenia	1 (12%)	1 (12%)	1
Anorexia	1 (12%)	0	4
TSH increase	1 (12%)	0	3
Hepatotoxicity	1 (12%)	0	1

[a]Median time after the start of the multikinase inhibitor to develop the adverse event

with sorafenib tended to develop early (within 3 months of treatment), diarrhea and weight loss occurred 6 and 7 months after sorafenib initiation. In DTC patients, the onset of diarrhea after sorafenib occurs usually later than in other tumor types [21, 22]. The number of patients that received lenvatinib in our cohort was low. Hypertension, diarrhea, hand–foot skin reaction, and proteinuria were the most common AEs, consistent with what was observed in the SELECT trial [4].

Only one patient (4.5%) in our cohort had to stop definitively sorafenib treatment due to a severe AE (heart failure) after 9 months of treatment and it resolved after MKI withdrawal. Another patient had a 10% decline in left ventricular ejection fraction (grade 2 AE), which occurred 2 months after the initiation of sorafenib treatment. It improved after dose reduction of the drug. VEGFR inhibitor therapy showed an incidence of all-grade and high-grade congestive heart failure of 3.2% and 1.4%, respectively [23].

The only patient in our cohort who had to stop sorafenib treatment eventually died suddenly. This was probably not related to the MKI treatment because her ejection fraction had improved after sorafenib withdrawal and her death occurred 5 months after the AE. No AE-related deaths were documented in our study.

Limitations to our study include its retrospective nature and the small sample size, although this is the largest experience presented by a single center in Argentina. Also, the median duration treatment with lenvatinib was low (2.9 months), which did not allow proper assessment of responses with this treatment.

In summary, we present in this study the experience of an Endocrinology Division on the use of MKIs and the management of the AEs produced by the two approved drugs for RAI-refractory DTC patients. The PFS in our group of patients who received MKI therapy was 31.5 months, which is longer than that reported by clinical trials and other cohorts [3, 4, 8, 10]. These agents appear to be useful in patients with advanced and progressive DTC, probably also extending the OS. Although virtually all patients experience AEs, most of them are manageable and rarely a definitive withdrawal is necessary.

Compliance with ethical standards

Conflict of interest Fabián Pitoia is medical advisor, speaker and Steering Committee Bayer. Consultancy for Sanofi and Raffo Laboratories. The remaining authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Institutional Review Board.

Informed consent Informed consent was obtained from all individual participants included in the study.

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