Iran J Nucl Med. 2023;31(1):42-48 [Serial No. 60]

Homepage: https://irjnm.tums.ac.ir/

ORIGINAL RESEARCH ARTICLE

Clinical benefit and quality of life during low-dose sorafenib maintenance therapy in radioiodine refractory differentiated thyroid cancer patients: A historical cohort study

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ARTICLE INFO

Article History:
Received: 16 June 2022
Revised: 23 September 2022
Accepted: 24 September 2022
Published Online: 17 October 2022

Keyword:
Multikinase inhibitors
Sorafenib
Differentiated thyroid cancer
Radioiodine treatment
Progression free survival

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ABSTRACT

Introduction: Effective management of radioiodine (RAI)-refractory differentiated thyroid cancer is a challenge due to limited treatment options. Multikinase inhibitor therapy including sorafenib has been an optional treatment in recent years. This study aims to compare the clinical benefit rate, progression free survival, and quality of life between patients who received limited dose of sorafenib (200-400 mg per day) as opposed to the control group.

Methods: Twenty-two patients who received sorafenib and twenty-three cases in the control group were studied for two years. Baseline variables were comparable between two subgroups. The results of diagnostic imaging methods were also taken into consideration. Quality of life was measured using the EORTC (European Organization for Research and Treatment of Cancer) quality of life questionnaire.

Results: Based on the RECIST (Response Evaluation Criteria in Solid Tumors) criteria, clinical benefit rate was 77.3% and 47.8% in sorafenib and control subgroups respectively (p value=0.042). The median of progression free survival for the sorafenib subgroup was 24 months and in the control subgroup was 22 months (p value=0.020). In a comparison between two groups regarding their quality of life, all subscales were statistically insignificant between the two groups except for the symptom subscale (p value=0.001).

Conclusion: Low-dose sorafenib maintenance therapy is an effective treatment option in RAI- refractory differentiated thyroid cancer with the main effect of stabilizing the disease. Except for unpleasant but tolerable adverse effects, this treatment has no significant negative influence on the quality of life as far as the physical, role, cognitive, emotional, financial and social functions are concerned.

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How to cite this article: Fallahi B, Moharrami K, Beiki D, Fard-Esfahani A, Alimoghaddam K, Eftekhari M. Clinical benefit and quality of life during low-dose sorafenib maintenance therapy in radioiodine refractory differentiated thyroid cancer patients: A historical cohort study. Iran J Nucl Med. 2023;31(1):42-48.

https://doi.org/10.22034/IRJNM.2022.40039

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INTRODUCTION

Differentiated thyroid cancer (DTC) is the foremost common endocrine malignancy throughout the world. Principle treatment for these patients incorporates total or subtotal thyroidectomy with radioactive iodine (RAI) ablative treatment. In DTC patients up to 5–10%, that is 6–7 new cases/year/million develop metastatic disease, mostly in lungs and bones besides, two-thirds of these tumors (4–5 new cases/year/million) lose their capacity to uptake radioiodine because of dedifferentiation and become RAI refractory; their 10-year survival rate is then reduced to less than 20% [1]. Resistance to treatment is more pronounced in older ages, patients with extensive metastases and those with high tumor avidity for [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) in positron emission tomography/computed tomography (PET/CT) [2, 3]. In these cases, treatment options include multiple ablative doses of RAI therapy, radiotherapy, surgical metastasectomy and so on. Thyroid tumors are highly vascular and overexpress vascular endothelial growth factor (VEGF). In addition, inhibition of VEGF receptor (VEGFR) signaling has been shown to inhibit growth of thyroid tumors, thereby providing a strong rationale for targeting VEGFR in this disease [4]. In recent years, new therapeutic drugs with molecular targets have been presented. The American Thyroid Association (ATA) guideline provides recommendations for the treatment of radioiodine refractory patients using multikinase inhibitors (MKIs) [2]. The most widely used drug is sorafenib. Sorafenib targets C-RAF, B-RAF, VEGF, PDGF receptor-β, RET, c-kit, and Flt-3 receptors [5]. Gain of function mutations in the BRAF oncogene are the most frequent genetic alterations found in PTC, occurring in approximately 45–70% of these tumors in adults [6]. There is no definitive conclusion on the effectiveness of this drug on the overall survival benefits [7, 8]. In general, the challenge of using MKI therapy is still present mainly due to the side effects of these drugs. The main issue is to determine the correct time to start using these drugs and also properly select the patients who benefit from this treatment properly [9-11]. The recommended dose for the initiation of treatment of progressive RAI-RTC patients is 800 mg per day [12]; however, this dose may be intolerable in many patients as many complications (i.e. dermatologic toxicities, renal impairment, hepatic impairment and gastrointestinal complications) may occur at the beginning of therapy unpromising the patient for continuing the treatment. In addition to the outcome, the patient's tolerance for continuing the treatment is also of concern. Thus, the main purpose of this study is to evaluate the effect of limited dose of sorafenib (200-400 mg per day) on the biochemical and structural response as compared to the control group. Another issue about these patients is the quality of life (QoL), which is less discussed in the literature. RAI-RTC are divided into four groups based on the ATA guideline [2]. The patients in this study will be enrolled according to the same guideline.

METHODS

Study population

According to the ATA guideline, the study population includes patients with differentiated metastatic thyroid cancer, who are in one of four groups: (1) Tumor tissue does not absorb iodine from the beginning. (2) Tumor tissue loses the ability to absorb iodine in the course of the disease. (3) Iodine is absorbed in some metastases and not absorbed in some others. (4) The disease has metastatic progression despite iodine uptake [2].

Patients were divided into two groups based on whether they received treatment with sorafenib (exposed group) or not (control group). The minimum course of treatment in the exposed group was six months and the dose was 200-400 mg per day. The dose for the treatment was 400 mg and in the case of intolerable complications, the dose was de-escalated in to 200 mg per day. All patients were followed every six months during the 2-year period after the course of the treatment. The control group was selected from RAI-RTC patients who were not received sorafenib treatment and were matched with exposed group regarding the baseline conditions including age, sex, subtype of DTC in the primary pathology report, size of the primary tumor, number of iodine therapies, location of the metastatic lesions and the baseline thyroglobulin (Tg). Radiological evaluation is basically performed with CT scan. Other modalities such as neck sonography and [^{18}F]FDG PET/CT were used whenever available. The study was approved by the local ethics committee of Tehran University of Medical Sciences under the approval number of IR.TUMS.MEDICINE.REC.1399.348.

For confirming the comparability of the two groups, intervening underlying variables were compared so that the two subgroups were not significantly different.

Follow up evaluation and outcome

The endpoint was defined according to the follow up Tg measurements and imaging results (i.e. neck sonography, CT scan and [^{18}F]FDG PET/CT). Patients were classified according to biochemical and structural criteria into the complete response (CR),

partial response (PR), stable disease (SD) and progressive disease (PD) groups [13]. Complete response was defined as the disappearance of all lesions and normalization of the tumor marker while partial response was defined as a reduction of at least 30% in the maximum diameter of the lesions with any Tg level. Progressive disease when at least 20% increase in the diameter of the lesions or the appearance of one or more new lesions or more than 50% increase in the serum Tg level is seen. Stable disease is defined as the size of the lesions don't grow enough to be categorized in PD subgroup and don't reduce as much as being classified in PR subgroup. Clinical benefit is defined as the sum of CR, PR and SD. Progression free survival (PFS) was calculated as the time interval (months) during which the disease did not progress. QoL was assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).

Statistical analysis

All normally distributed quantitative data were expressed as mean±standard deviation. If the quantitative data was not normally distributed, non-parametric test (Mann-Whitney test) was used to compare the data between two groups. Corresponding tables were used for qualitative data in different groups, and the χ^2 test was used to analyze this data in different groups. PFS curves were plotted and Kaplan-Meyer test was used to compare the PFS between two subgroups. Statistical analysis was performed using dedicated software (SPSS 26.0; IBM Corp., Armonk, NY). All results of statistical tests were considered significant at the level of $p < 0.05$.

RESULTS

Twenty-two patients in the sorafenib subgroup and twenty-three control cases were evaluated. The comparison of the baseline variables between the two studied subgroups is shown in (Table 1). There was no statistically significant difference in terms of all baseline variables (including age, gender, initial risk of DTC based on pathology report, cumulative dose of previous RAI therapies and baseline serum Tg) between the two subgroups.

Among patients treated with sorafenib 17 (77.3%) had pulmonary metastasis, 4 patients (18%) had lung and bone metastases and one patient (4.7%) had only bone metastases. Among the control group, 17 patients (73.9%) had lung metastasis, 2 patients (8.7%) had lung and bone metastases, 2 (8.7%) had cervical and mediastinal lymph node metastases and 2 patients (8.7%) had only bone metastases.

Table 1. Comparison of baseline variables between the two subgroups (the group treated with sorafenib and the control group)

Baseline Variable		Exposed Group N=22	Control Group N=23	P-value
Age	Mean ± SD	67.3±7.6	63.9±9.1	0.280 (NS)
Gender	M/F	10/12	8/15	0.335 (NS)
Initial Risk based on ATA classification (%)	Intermediate/High	14/8	16/7	0.673 (NS)
No. ofradio-iodine treatment	<3 3-6 >6	3 (13.6 %) 18 (81.8 %) 1 (4.5 %)	4 (17.4 %) 14 (60.9 %) 5 (21.7 %)	0.193 (NS)
The cumulative dose of previous RAI therapies (mCi)	Mean ± SD Median Range	760±316 750 200-1550	803±393 650 325-1550	0.909* (NS)
Primary serum Tg (ng/dl)	Mean ± SD Median Range	153±105 181 1-281	108±103 73 3-250	0.080* (NS)

ATA: American thyroid association [2]
RAI: Radio-active iodine
NS: Not significant
SD: Standard deviation
*: Non-parametric comparison between groups (Mann-Whitney U test)

The initial risk was intermediate in 14 patients and high in 8 patients according to the 2015 ATA guideline classification in the sorafenib subgroup. Among the patients in the control subgroup 16 were determined as intermediate risk and 7 as high risk (p-value = 0.673).

Comparing the response to treatment based on the defined criteria as shown in (Figure 1), in the subgroup of patients treated with sorafenib, 2 (9.1%) had a partial response, 15 (68.2%) had stable disease and 5 (22.7%) had progression. In control subgroup, 2 (8.7%) patients had a partial response, 9 (39.1%) patients had stable disease, and 12 (52.2%) patients had progression. No case in either group received a complete response to treatment (p-value = 0.113).

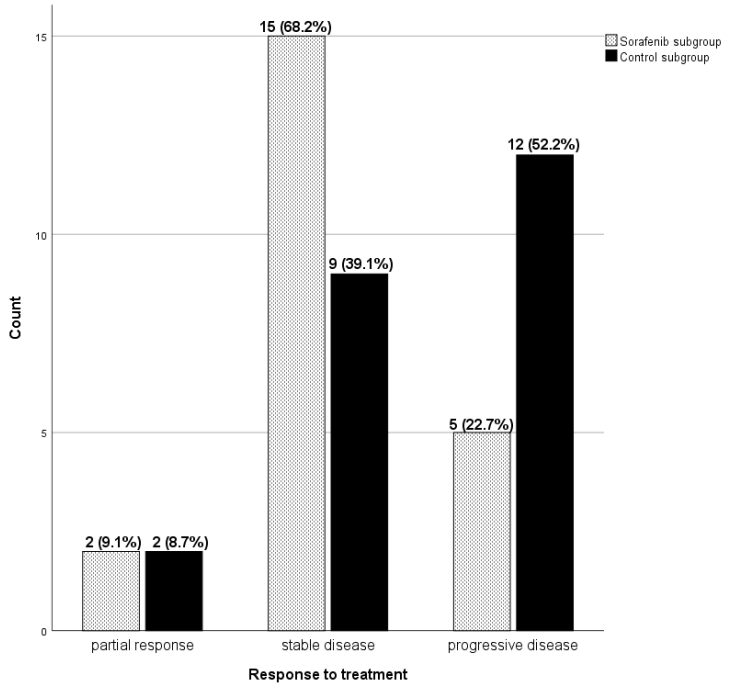

Fig 1. Comparison of treatment response between sorafenib and control groups

Clinical benefit rate, which was defined as summation of CR, PR, and SD (Table 2) was 17 among 22 patients (77.3%) in the sorafenib subgroup and 11 from 23 patients (47.8%) in the control subgroup (p-value = 0.042).

Table 2. Comparison of clinical benefit rate and progression-free survival in patients treated with sorafenib and control group

		Sorafenib subgroup N=22	Control subgroup N=23	P-value
Clinical benefit rate		17 (77.3%)	11 (47.8%)	0.042*
Progression-free survival (months)	**Median**	24	22	0.020*
	Range	(10-24)	(6-24)	
*Statistical Mann-Whitney U test				

Median of PFS was 24 months (ranging between 10 to 24 months) in the sorafenib and 22 months (ranging between 6 to 24 months) in the control group (p-value = 0.020). The Kaplan-Meyer curve was shown in (Figure 2).

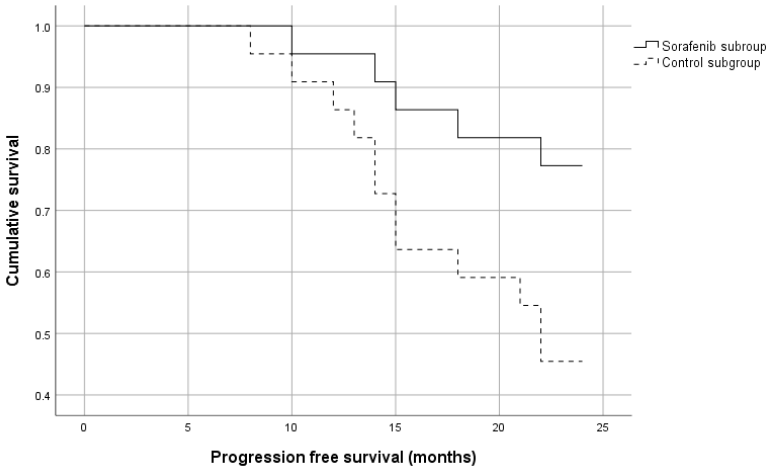

Fig 2. Comparison of progression-free survival between the groups treated with sorafenib and the control group

Using the standard EORTC survey, the following eight sub-scales of QoL between the two groups, Physical function, Role function, Symptom scale, Cognitive function, Emotional function, Social function, Financial function, Global function, and finally the sum of the subscales under the heading of Sum of scores were compared in (Table 3).

Table 3. Quality of life comparison between patients treated with sorafenib and control group

Subscale	Maximum Score	Sorafenib subgroup (N=22) Median score (range)	Control subgroup (N=23) Median score (range)	P-value
Physical function	20	15.5 (8-18)	15 (8-20)	0.631
Role function	8	6 (4-8)	6 (4-8)	0.473
Symptom scale	48	31.5 (25-40)	39 (30-43)	0.001
Cognitive function	8	8 (5-8)	8 (4-8)	0.754
Emotional function	14	9 (7-15)	8 (7-12)	0.153
Social function	8	7.5 (6-8)	6 (4-8)	0.114
Financial function	4	3 (3-4)	3 (2-8)	0.706
Global function	14	9 (6-12)	10 (7-12)	0.981
Sum of the scores	126	87.5 (66-106)	97 (73-112)	0.191

DISCUSSION

Treatment with MKI has shown promising results in RAI-RTC patients. Overall, our study indicates that sorafenib treatment in these patients is associated with favorable outcomes.

Among recent studies, an article evaluating the efficacy of sorafenib in RAI-refractory patients by Sousa Santos F et al confirmed that sorafenib with standard dose is an effective treatment for delaying disease progression in this group [14]. Also, in a study by Kloos RT et al, sorafenib was described as a well-tolerated treatment with clinical and biological antitumor effects [15]. Additionally, in a systematic review by Nigel Fleeman et al, 92 articles including two randomized controlled clinical trials were reviewed regarding the effectiveness of sorafenib treatment. Overall, sorafenib with a predefined dose of 800 mg was useful in improving objective tumor response as well as PFS [16].

Only limited number of studies are conducted to evaluate the low-dose or modified dose of sorafenib for the treatment of RAI-RTC patients open for future investigations. In a study by Libo Chen et al, low-dose treatment was suggested with acceptable response to treatment associated with less and tolerable complications. The major limitation of this study was small sample size (9 patients) [17].

Also, in a study by Ramona Dadu et al the authors concluded that the efficacy of the sorafenib treatment with dose of less than 800 mg was not significantly differed from standard dose of 800 mg [18].

These results are in accordance with our findings showing that the rate of response to treatment in sorafenib group with low-dose treatment was significantly higher than the control group. Also the group treated with low-dose sorafenib had a higher clinical benefit rate.

Another aim of our study was to compare the PFS rate between the two subgroups. Based on the results of this study, it seems that as mentioned in previous studies, the use of sorafenib, even with limited dose of 200- 400 mg, significantly increases the PFS. A double-blinded randomized clinical trial by Marcia S Brose et al, showed similar results [19]. Based on a retrospective study in 2021 by Chen Yuan Lin et al in Taiwan, the use of sorafenib in DTC patients who are resistant to RAI was effective in improving PFS [20].

Regardless of the efficacy of the treatment with sorafenib in RAI-RTC reported by most of the investigators, the issue of starting and maintenance doses which optimally balance between benefit and adverse effect is controversial so far. In our study, the maintenance dose of 200-400 mg per day revealed better outcome and higher PFS as compared with drug-naïve RAI-RTC patients; however, data about starting dose was unavailable in some patients. On the other hand, more comparative studies are needed to optimize the starting and maintenance doses considering the safety, tolerability and efficacy of sorafenib.

Another purpose of this study, which is less discussed in the literature, was to compare the QoL between two groups. According to the results of our study, there is no significant difference in the overall scale of QoL between the two groups. Among the subscales studied including 8 scales, physical function, role function, symptom scale, cognitive function, emotional function, social function, financial function and global function, there was only difference in the results of the “symptom subscale”. It seems that this may be due to the unpleasant side effects of sorafenib even in low-dose treatment [2, 9]. In a 2021 study conducted by Alice Nervo et al on QoL during treatment with lenvatinib for thyroid cancer

patients, they concluded that QoL decreased during the first months of therapy; nevertheless, patient's well-being seemed not to be worsened by the cumulative toxicity of the drug over time and QoL was restored after 12 months of therapy [21]. Another study by Razavi Ratki SK et al about quality of life assessment in DTC on 435 patients revealed that QoL scores are affected by the majority of socio-economic factors as well as treatment and follow up variables [22]. Further studies are needed on the QoL of RIA-refractory patients receiving multikinase inhibitor therapy.
A notable shortcoming in our study same as the most currently published data, is that some interfering variables are less controlled in historical cohort studies when compared with double-blind randomized clinical trials. Given the ethical considerations in dividing patients into treatment and control subgroups, this study was performed as a cohort and tried as much as possible to match the two groups in terms of clinical status and other interfering or confounding factors. Additionally, one more limiting factor of our study was the small sample size.

CONCLUSION

Treatment with MKI, including sorafenib, may be considered for the treatment of patients with DTC who are resistant to RAI therapy. Based on the results of our study, this treatment with low maintenance dose of 200-400 mg per day have significant influence on stabilizing the disease and prolonging PFS. Another issue about these patients is the QoL which does not seem to be significantly different from those who are not under treatment with this drug. Considering the importance of patient's compliance for continuing the treatment, QoL and overall health, low-dose sorafenib maintenance therapy may provide a reasonable approach for the management of patients with RAI-refractory DTC.

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