Multimodal Prehabilitation in Radioactive Iodine-refractory Differentiated Thyroid Cancer Treated With Lenvatinib.

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Abstract

Purpose

This study describes our clinical experience with lenvatinib for the treatment of radioactive iodine refractory differentiated thyroid cancer (RR-DTC) using a multimodal patient-centered prehabilitation multidisciplinary approach assessing its effectiveness and patient outcomes.

Methods and design

This is a retrospective observational real-life study of a consecutive series of RR-DTC patients treated with lenvatinib as first-line treatment at Germans Trias i Pujol University Hospital.

Results

Partial response was observed in 6 patients (46.1%), stable disease in 5 patients (38.5%) and disease progression in 2 patients (15.4%). PFS and OS were 16.3 and 17.9 months respectively. AEs occurred in all patients. The most common adverse event (AE) was fatigue (69%), followed by diarrhea (46%), hypertension (46%) and anorexia (38.3%). Weight loss was present in 30.7% of the patients and only 7.7% was grade 3.

Conclusion

In our experience, prehabilitation can be useful to decrease not only the incidence but the severity of important side effects such as weight loss, anorexia and hypertension. For these complex patients, a multidisciplinary team is useful for follow-up, treatment and prevention of possible AEs.

Introduction

Differentiated thyroid cancer (DTC), which includes papillary and follicular types, comprises the majority (>90%) of all thyroid cancers (1). Usually, DTC has a favorable prognosis but up to 15% of patients will develop metastatic disease and may become refractory to RAI (radioactive iodine) therapy (2,3). This radioactive iodine refractory situation limits therapeutic options and worsens prognosis (4). Novel target therapies, such as tyrosine kinase inhibitors (TKI), have proven to be successful in prolonging progression-free survival (PFS) in these patients (5). Lenvatinib is an oral multi-target TKI that acts on vascular endothelial growth factor (VEGF) receptors 1-3, RET and KIT proto-oncogenes, platelet-derived growth factor receptor-α (PDGFR), and fibroblast growth factor receptors (FGFR) 1-4 resulting in inhibition of cell proliferation. In 2015, after the SELECT trial (6), it was approved by the FDA for the treatment of locally recurrent or metastatic progressive radioactive iodine refractory differentiated thyroid cancer (RR-DTC). The SELECT trial was a randomized, double-blind, phase III trial aimed to compare lenvatinib 24

mg daily vs placebo in RR-DTC patients. Lenvatinib was associated with significant improvements in PFS, with a median of 18.3 months compared to 3.6 months in the placebo group. The lenvatinib group also had a significant 64.8% improvement in the response rate compared to 1.5% in the placebo group. On the other hand, as a result of its mechanism of action, specifically by inhibiting the VEGF pathway, various adverse effects (AEs) have been described occurring in almost all patients (7). The most relevant lenvatinib-associated AEs were hypertension (67.8%), diarrhea (59.4%), fatigue and asthenia (59%), decreased appetite (50.2%), weight loss (46.4%), and nausea (41%), and 7% were fatal.

Real-world data support the results found in the SELECT trial. A French retrospective study involving 75 RR-DTC patients with a median follow-up of 7 months reported that AEs were present in 95% of them, being the most frequent fatigue, hypertension, weight loss, diarrhea, and anorexia (8). Moreover, in a compassionate use of lenvatinib, a study of the first patients treated in Italy established that the drug is active and safe in unselected RR-DTC patients. Most common AEs in this latter study were fatigue and hypertension (9). In the RELEVANT study (10), a retrospective multicentric study of real-world data in Austria found that in 43 patients with metastatic RR-DTC, lenvatinib showed sustained clinical efficacy even with reduced maintenance dosages over years (OS 63% with a daily maintenance dosage $\leq$ 10 mg/day vs. 82% with $\geq$ 14 mg/day). In this study, Grade $\geq$3 AEs (hypertension, diarrhea, weight loss, and palmar-plantar erythro-dysesthesia syndrome) were the most common leading to discontinuation of lenvatinib in 16% of the patients.

Given the limited therapeutic options together with the frequency and severity of AEs, these patients have a complex management. A multidisciplinary team approach can ensure safe and effective use of lenvatinib and it is relevant asserting a good quality of life throughout the treatment (1). Cancer prehabilitation is a process from cancer diagnosis to the beginning of the treatment, which includes psychological, physical and nutritional assessments, identification of comorbidities, and targeted interventions aiming to improve the patient's health and functional capacity. A multimodal prehabilitation program has been described as an efficient tool in oncological surgery, achieving meaningful changes in postoperative functional exercise capacity (11). Multimodal prehabilitation may include exercise, nutritional counseling, psychological support, and optimization of underlying medical conditions, as well as cessation of unfavorable health behaviors such as smoking and drinking (12). Currently, there are no standardized guidelines for prehabilitation in DTC, and the existing studies are heterogeneous. However, multimodal approaches are likely to have a greater impact on functional outcomes than single management programs.

Studies reporting multimodal prehabilitation in thyroid cancer are scarce. The main objective of this paper is to describe our clinical experience with lenvatinib for the treatment of RR-DTC using a multimodal patient-centered prehabilitation multidisciplinary approach assessing its effectiveness and patient outcomes.

Materials And Methods

Study design

This is a retrospective observational real-life study in which we reviewed the clinical data of a consecutive series of patients treated with lenvatinib at Germans Trias i Pujol University Hospital. Clinical data, AEs and patient outcomes status were assessed at the last follow-up visit. RR-DTC was defined according to the European Thyroid Association Guidelines (13) by structural progression occurring within 6-12 months after RAI administration or lack of RAI concentration of distant metastases. Inclusion criteria were confirmed diagnosis of RR-DTC and initiation of lenvatinib as a first-line treatment. The study was conducted in accordance with the Declaration of Helsinki and and was approved by the local Human Research Ethics Committee of the Hospital Germans Trias i Pujol. All participants gave their written informed consent.

Initiation and follow-up

Lenvatinib was started with an initial dose of 24mg/day. Dosage was adjusted according to the disease evolution and AEs occurrence.

During the treatment, visits were established according to the patient's clinical status, with a frequency ranging from weekly to monthly basis. When the patient was stable enough, visits were spaced every 3 months. If the patient required urgent attention he/she was visited in our outpatient clinic or in the emergency room.

In every visit, clinical status and AEs were assessed. AEs were graded from 1-4, from mild to potentially life-threatening according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, https://ctep.cancer.gov/ protocoldevelopment/electronic_applications/ctc.htm). If the patient suffered a severe AE, the drug was discontinued.

Multimodal prehabilitation and multidisciplinary approach

Our multidisciplinary team included thyroid and nutrition expert endocrinologists, registered dietitians, endocrine surgeons experts in thyroid cancer treatment, oncologists, phycologists, radiologists and nuclear physicians.

Prehabilitation was multimodal and based in four actions: medical optimization, physical intervention, nutritional and psychological intervention. The protocol started three to four weeks before lenvatinib treatment.

Medical optimization

In this action, pre-existing comorbidities were identified and managed before starting lenvatinib treatment. These included tobacco and alcohol consumption, frailty evaluation, treatment of anemia, and therapeutic optimization of other chronic diseases. Daily register of blood pressure and weight was

indicated. Due to very frequent lenvatinib-associated hypertension, this condition was treated and optimized before lenvatinib initiation. When severe, AEs were evaluated by a specific reference specialist.

Nutritional intervention

Patients were evaluated by a registered dietitian. Dietary habits and anthropometric data were evaluated in each visit. Nutritional status, assessed by the Patient-Generated Subjective Global Assessment (PG-SGA) (14) was used to establish the diagnosis and severity of malnutrition. A personalized nutritional program was designed for each patient, including food selection and meal planning. Energy and protein requirements were calculated following the European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines for cancer patients (15). Energy targets ranged between 25 and 30 kcal/kg/day and protein targets between 1.2-1.5 g/kg/day. If oral dietary intake remained inadequate despite dietary advice, oral nutritional supplements (ONS) were started. Grade 1 (G1) weight loss was considered if the percent of weight loss after 6 months from baseline was ≥5-10%, grade 2 (G2) 10-≤20% and grade 3 (G3) ≥20%. The accomplishment of the adherence to diet and ONS was monitored during the follow-up.

Exercise Program

Physical activity was also included in the prehabilitation program. Individually adapted intensity exercise was recommended for all patients. This home-based exercise program consisted of daily sessions of aerobic, strength and respiratory exercises. Aerobic exercise included moderate daily continuous walk and jogging or cycling training 3 days per week adapted to individual physical capacity. Strength training consisted in daily 15-minutes of 8-10 repetitions for large muscles, by using patient-adapted weights or elastic bands and squats. If intense fatigue (grade >2) occurred during the treatment, patient was reevaluated physically and biochemically by a specialist in physical medicine and rehabilitation.

Psychological intervention

Patients were evaluated by the home care program and support team that included physicians and psychologists with experience in oncological diseases. Psychological status was assessed by means of an interview in which affective or mood disorders and anxiety levels were evaluated. Family and social environment were also assessed. Personalized pharmacologic treatment and psychological support were prescribed to reduce anxiety or depression. These patients were followed up by psychologists according to the intensity of the symptoms.

Data Analysis

Numerical data are described with median, mean, standard deviation (SD), quartiles and percentages as appropriate. PFS and OS were evaluated using Kaplan-Meier estimates with 95% confidence intervals (CI). PFS was defined as the duration between the beginning of the drug (lenvatinib) until disease progression or death. OS was calculated from the beginning of the drug to the patient's death or date of the last follow-up. All statistical analyses were performed with IBM SPSS Statistics software version 26 (IBM Corporation, New York, USA) and Excel Microsoft**.**

Results

We reported the results of 13 patients with RR-DTC treated with lenvatinib in our institution. The majority of them were female (69.2%) and had a mean age of 67 years old (SD=12 years) at the initiation of lenvatinib treatment. According to the American Joint Committee on Cancer (AJCC), the majority of patients were stage IV (75%). Almost all patients underwent surgery except one who had unresectable disease at diagnosis. The most frequent histological type was papillary DTC followed by follicular DTC and Hürthle cell. Of the papillary group, 2 were follicular subtype and 2 had poorly differentiated areas (Table 1). Previous to systemic treatment, 72.7% of the patients had been treated with RAI therapy with a mean cumulative dose of 257□139 mCi. All patients were treated with levothyroxine to achieve TSH suppression (average dose 136 mcg/day). Lenvatinib was initiated as a first-line (1L) treatment for all patients. Mean time from diagnosis to initiation of 1L was 71.3 ± 56.2 months. Mean duration of the treatment was 16.6 months (SD=14.3). Dose reduction was required in 69.2% of the patients on a daily basis. Mean time to new dosage was 21.8 weeks (SD=21.2). Lenvatinib was discontinued in 23% of patients as a result of toxicity and of disease progression. Patient's characteristics are described in Table 1.

Partial response was observed in 6 patients (46.1%), stable disease in 5 patients (38.5%) and disease progression in 2 patients (15.4%). PFS and OS were 16.3 and 17.9 months respectively.

AEs occurred in all patients. The most common AE was fatigue (69%) followed by diarrhea (46%), hypertension (46%) and anorexia (38.3%). Most of them were G2 AEs. Severe AEs included upper gastrointestinal bleeding and proteinuria. No fatal AEs were observed. Table 2 summarizes all AEs in our cohort. Fatigue that occurred in 69% patients was treated with exercise and if intense it was evaluated by a specialist in physical medicine and rehabilitation. Hypertension occurred in 46% of the patients, most of them received more than one antihypertensive drug. One patient presented hypertension and proteinuria in the context of a nephrotic syndrome and was evaluated and followed by a nephrologist. In this patient, lenvatinib treatment was withdrawn and restarted after renal function recovered. Diarrhea was treated and controlled with dietary advice and pharmacological intervention (loperamide). ONS were initiated in more than half of the patients (54.5%). Hypercaloric hyperproteic polymeric formulas were used. Only 2 patients needed semi-elemental formulas to increase gastrointestinal tolerance. Weight loss was present in 30.7% of the patients and only 7.7% was G3. At baseline 23% of the patients were moderate malnourished (stage B of PG-SGA) and after a 6 months follow-up 38.4% of them were malnourished, 30.7% moderate and 7.6% severely malnourished (stage B and C of PG-SGA respectively). In two patients, megestrol acetate was used to increase appetite. In other gastrointestinal AE (dyspepsia, nausea) symptomatic treatment was started. Less common side effects included one case of adrenal insufficiency and pancytopenia.

Discussion

To our knowledge, this is the first report in our country evaluating the real-world experience with multimodal prehabilitation in the management of lenvatinib-treated RR-DTC patients. Compared to the SELECT trial (6), in which specific prehabilitation protocol was not applied, our findings regarding AEs appearance were similar with fatigue, hypertension and diarrhea being the most common toxicity events. Although fatigue was frequent in our patients, it was well tolerated and only one-third of the patients was G3. Remarkably, weight loss and anorexia were lower in our cohort (30.7% *vs.* 46.4%, and 38.3% *vs.* 50.2%, respectively). Compared to other real-life studies, weight loss and anorexia are also lower in our cohort. ONS and frequent follow-up by a registered dietitian as well as the physical activity program proposed to these patients probably attenuated muscle strength loss and development of sarcopenia related to treatment in our patients.

In one case adrenal insufficiency was diagnosed after the patient reported intense fatigue, which indicates that it is also recommendable to measure cortisol levels in these cases. As patients kept a daily log of blood pressure, we could early detect and treat hypertension, having a lower prevalence ≥G3 (15.3% *vs.* 41.8%) compared to the SELECT trial.

Since its approval in 2015, lenvatinib has been used as first-line treatment for RR-DTC in our institution. Regarding effectiveness, our results are comparable with other reports based on the clinical practice. In our series, partial response was observed in 46.1% of the patients, higher than the French and Italian studies (31% and 36% respectively) (8,9). Progression at the moment of the results evaluation in our cohort (15.4%) was similar to these studies (14% in both series). Moreover, our PFS rate was one month higher than the one observed in the SELECT study (16 and 15 months respectively) and was also higher when compared to other reported real-world data (8,9,16).

Few studies have reported the use of prehabilitation in thyroid cancer. Prehabilitation was first described by Silver and Baima (17) and defined as the targeted interventions before the beginning of acute treatment aimed to reduce the incidence and severity of current and future impairments related to primary therapy and natural disease evolution. These programs have been used mainly before orthopedic surgery with improvement of health outcomes (18). In oncologic patients, prehabilitation has been used as a useful tool to improve patient's evolution, but mainly before surgical intervention (19), and its positive effects on the quality of life (QoL) as well as general outcomes have been also described in elderly cancer survivors (20). Reports on the benefits of prehabilitation in non-surgical cancer patients are scarce. Limited data for multimodal prehabilitation programs with exercise and nutritional interventions in patients with cachexia reported improvements in physical endurance and depression scores (21). To date, there is no data regarding prehabilitation in RR-DTC.

As mentioned before, real-world studies support the efficacy of lenvatinib in the treatment of RR-DTC, but with the frequent appearance of important AEs that difficult the maintenance of the recommended doses (22-24). Based on this, a multidisciplinary approach with the participation of various specialties is recommended to detect and treat AEs quickly and efficiently, or even better, to avoid or diminish their appearance. In our study, when compared to other studies where prehabilitation was not applied, we

showed that it can reduce the incidence of side effects that can be limiting for cancer treatment, such as anorexia and weight loss. In our series, 23% of the patients presented moderate malnutrition in accordance with the results of a prospective Spanish observational study in which it was evidenced that 21.7% of the patients treated with TKI presented moderate malnutrition, and that this was related to a lower survival four years after diagnosis (25). The nutritional intervention in our patients started with the evaluation of the patient's initial nutritional status and was based on a balanced diet and a sufficient protein intake, increasing energy foods and meal frequency according to ESPEN guidelines (26). ONS were started if necessary. Given that 23% of the patients were malnourished before starting the treatment, periodic screening of nutritional state is necessary from the beginning of the diagnosis to identify which patients need nutritional support.

Moreover, the baseline functional level was also used individually to indicate the prehabilitation exercise program. Physical activity can modulate human proteome and transporters with positive effects in structural and functional muscle performance and counteract the AEs of cancer treatments (27). In our protocol, structured, simple and easy to follow recommendations were proposed for each patient under a personalized approach at baseline and during the follow-up. As previously demonstrated, exercise increases muscle and plasma protein synthesis in younger and older men (28), patients were encouraged to eat protein supplements immediately after strength. Fatigue is known to produce significant negative effect on QoL and its prevention should be a priority in cancer therapy strategies (29). With the combination of nutritional and physical training actions in our group of patients treated with lenvatinib, fatigue and asthenia appeared but with moderate intensity, and no dose reduction or withdrawal of the drug was necessary in relation to this symptom.

Patients suffering from cancer and its related comorbidities and the side effects of cancer drugs had different levels of stress, depression and anxiety that may themselves influence the prognosis (30). In this sense, targeted interventions to increase patient's psychological resilience have demonstrated an improvement in QoL and adherence to treatments (31). Regarding the psychological actions in our protocol, they focused on the disease acceptance by the patients and their empowerment, so that they can face a treatment that can produce more symptoms than the neoplastic disease itself; early detection and rapid treatment of mood disorders was essential for protecting QoL in these patients. The self-reported level of well-being during the follow-up in our cohort, the tolerance to fatigue and the adherence to the treatment point towards a beneficial effect of the psychological interventions performed.

LIMITATIONS

Our report has some limitations. The main one is that it includes a relatively low number of patients and that its retrospective and observational design but its real-life nature provides, in our opinion, interesting data about the management of TKis in RRTC patients. The lack of a control group was decided for ethical reasons given the expected beneficial effects of the prehabilitation protocol.

Conclusion

In our experience, prehabilitation can be useful to decrease not only the incidence but the severity of important side effects such as weight loss, anorexia and hypertension. In these complex patients, a multidisciplinary team is useful for the follow-up, treatment and prevention of possible AEs and should constitute the standard of care of cancer patients, including those suffering from RR thyroid cancer treated with TKIs.

Declarations

The authors have nothing to declare.

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Conflicts of interest: The authors report no conflicts of interest.

Availability of data and material: The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Authors' contributions: All authors contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

Ethics approval: The study was conducted in accordance with the Declaration of Helsinki and was based on real life clinical practice.

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

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Tables

Table 1. Patient's clinical characteristics.

Gender (%)	
Female	69.2
Male	30.8
Age at initiation of lenvatinib (mean, SD)	67, 12
Histological subtype of DTC (%)*	
Papillary	83.4
Follicular	8.3
Hurthle Cells	8.3
AJCC stage (%)*	
I	0
II	0
III	25
IV	75
Metastasis disease at initiation of lenvatinib (%)	
None	0
Lymph nodes	38.4
Local	7.7
Distant	53.9

*n=12. DTC: differentiated thyroid cancer, SD: standard deviation

Table 2. Adverse events during treatment with lenvatinib.

Adverse Event	G1	G2	G3	G4	Total
Fatigue	23	23	23	0	69
Diarrhea	7.7	23	15.3	0	46
Hypertension	15.3	15.3	15.3	0	46
Anorexia	15.3	15.3	7.7	0	38.3
Weight loss*	7.7	15.3	7.7	0	30.7
Nausea	7.7	15.3	0	0	23
Headache	7.7	7.7	0	0	15.4
Hand desquamation	15.3	0	0	0	15.3
Dyspepsia	7.7	7.7	0	0	15.4
Polyglobulia, pancytopenia	0	15.3	0	0	15.3
Hemoptysis sputum	7.7	7.7	0	0	15.4
Rash	0	15.3	0	0	15.3
Hand-foot syndrome	7.7	0	0	0	7.7
Gingivitis	7.7	0	0	0	7.7
Dyslipidemia	0	7.7	0	0	7.7
Nephrotic syndrome	0	0	0	7.7	7.7
Dyspnea	7.7	0	0	0	7.7
Upper gastrointestinal bleeding	0	0	0	7.7	7.7
Adrenal insufficiency	0	7.7	0	0	7.7
Oral blistering	7.7	0	0	0	7.7
Dysgeusia	7.7	0	0	0	7.7

Percentages were calculated according to the total number of patients (N=13). *Weight loss after 6 months. AE: adverse event, G1: grade 1 (Mild AE), G2: grade 2 (Moderate AE), G3: grade 3 (Severe AE), G4: grade 4 (Life-threatening or disabling AE).