Antitumour Effects of Apatinib in Progressive, Metastatic Differentiated Thyroid Cancer (DTC)

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Research Article

Keywords: metastatic differentiated thyroid cancer, apatinib, tyrosine kinase inhibitor, radioactive iodine (RAI)

Posted Date: March 7th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1398865/v1>

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Abstract

Purpose: Management of progressive, metastatic radioactive iodine refractory differentiated thyroid cancer (RAIR-DTC) has been a great challenge due to its poor prognosis and limited treatment options. Recently, apatinib, an orally anti-angiogenic tyrosine kinase inhibitor (TKI) is reported to be useful for treatment of progressive RAIR-DTC. The aim of this study was to evaluate the antitumour effect of apatinib and the combination therapy with radioactive iodine (RAI) in patients with progressive metastatic DTC.

Methods: Five patients (all female, mean age 62 ± 8 years, ranged from 51 to 69 years) with progressive distant metastatic DTC (dmDTC) after total thyroidectomy (TTE) and neck lymph node dissection were treated with apatinib at a dose 500 mg per day after ^{18}F -Fluorodeoxyglucose (^{18}F -FDG) PET/CT. The effects of apatinib on DTC were evaluated at 4 ± 1 months after treatment with apatinib. RAI therapy was then initiated. The response to apatinib and the combination therapy with RAI treatment was evaluated by Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) and metabolic activity using serum thyroglobulin (Tg) and ^{18}F -FDG PET/CT.

Results: Positive ^{18}F -FDG PET/CT results were found in all patients before apatinib therapy. The immunohistochemical analysis of primary tumour tissues showed high expression of vascular endothelial growth factor receptor-2 (VEGFR-2). Four patients with follicular thyroid carcinoma (FTC) showed partial response (PR) with significant decrease in tumour size and maximum standardized uptake value (SUVmax) after 4 ± 1 month's treatment with apatinib. Further significant reduction of tumour size and SUVmax were observed in three patients after combination therapy with apatinib and RAI. Only one patient with both FTC and papillary thyroid cancer (PTC) demonstrated progressive disease (PD) after treatment with apatinib alone, however, a decrease in tumour size and SUVmax as well as serum Tg levels was achieved after the combination with RAI therapy and apatinib.

Conclusions: Apatinib had significant antitumour effects on progressive distant metastatic DTC. Moreover, beneficial synergistic and complementary effects were shown when apatinib combined with RAI therapy.

Clinical Trial Registration: NCT02731352, Registered April 7, 2016.

Introduction

Approximately 10–20% of differentiated thyroid cancer (DTC) patients have progress distant metastatic DTC (dmDTC) [1, 2]. A part of them belongs to radioactive iodine refractory DTC (RAIR-DTC) [1, 2]. The RAIR-DTC is leading cause of thyroid cancer related death [3]. The aggressive dmDTC presents a major management challenge. FDA has approved two agents targeting vascular endothelial growth factor receptors (VEGFRs), lenvatinib and sorafenib for treatment of RAIR-DTC [4, 5]. Although sorafenib and lenvatinib were found to prolong progression-free survival (PFS) in patients with RAIR-DTC, however, no significant benefit on overall survival (OS) was observed, except for a subgroup of patients older than 65

years in the SELECT trial [4, 5]. Therefore, alternative treatment options are needed for patients with RAI-R-DTC. Recently, our study showed that apatinib, a small-molecule tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor receptor 2 (VEGFR2) and platelet-derived growth factor receptor (PDGFR) β [6], demonstrates significant clinical benefits in both prolonged PFS and OS in patients with progressive locally advanced or metastatic RAI-R-DTC [7, 8]. In this preliminary study, we want to evaluate the role of apatinib on progressive distant metastatic DTC before RAI and the effects of combination therapy with RAI and apatinib.

Five patients, who had total thyroidectomy (TTE) and neck lymph node dissection before the study and at least one ^{18}F -Fluorodeoxyglucose (^{18}F -FDG)-avid progressive distant metastatic lesion as well as no previous RAI or TKI therapy, were included in the study. 500 mg Apatinib (Hengrui Medicine, Jiangsu, China) was administrated orally once daily until intolerable toxic effects occurred. Follow-up ^{18}F -FDG PET/CT was performed at 4 ± 1 months after apatinib treatment initiation and 3 months after further combination therapy with RAI and apatinib. Tumour response was evaluated according to RECIST (version 1.1) [9] and serum thyroglobulin (Tg) level as well as ^{18}F -FDG PET/CT (U780, United Imaging, Shanghai, China). Figure 1 showed the flow diagram of this study. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0). All adverse events were assessed every 4 weeks after apatinib was administration until the end of the study.

Case 1: A 64-year-old woman (No 1 in the Table 1) presented with pain in her left hip and right ribs with an increased serum Tg level of 8644 ng/mL. ^{18}F -FDG PET/CT showed high uptake in the thyroid masses and multiple lytic bone lesions on the right humerus, 10th right rib, and the left acetabulum accompanied by a large tumour infiltration (Fig. 2A, 2Aa, 2Ab, 2Ca and 2Cb). Follicular thyroid carcinoma (FTC) was diagnosed after a total thyroidectomy. High expression of VEGFR-2 was confirmed in immunohistochemical (IHC) analysis (Fig. 2F). Four months after apatinib treatment, ^{18}F -FDG PET/CT showed remarkable decrease in tumor size and ^{18}F -FDG uptake in metastases (Fig. 2B, 2Ba, 2Bb, 2Da and 2Db). Serum Tg level decreased to 887 ng/mL. Four cycles of RAI therapy were then performed with a total dose of 33,3 GBq (900 mCi) ^{131}I . Post therapeutic ^{131}I whole-body image showed radioiodine uptake in the bone metastases (not shown). Follow-up ^{18}F -FDG-PET/CT showed clearly further decrease in tumour size and reduced FDG uptake in bone lesions (Fig. 2Ea and 2Eb). The serum Tg level reduced to 6 ng/mL (Table 1).

Case 2: A 69-year-old woman (No 2 in the Table 1) had severe pain in her left hip. ^{18}F -FDG PET/CT showed ^{18}F -FDG-avid bone lytic lesion and tumour infiltration in the left ischium with serum Tg level of 12470 ng/mL. High expression of VEGFR-2 was confirmed with IHC analysis of the primary FTC after total thyroidectomy. Only three months after apatinib treatment, serum Tg level decreased to 3346 ng/mL. ^{18}F -FDG PET/CT showed markedly reduced metastatic tumour masses with reduced FDG uptake. After two cycles of RAI therapy with a total dose of 16.65 GBq (450 mCi) ^{131}I . Further tumour size decrease and metabolic activity reduction were demonstrated and Tg level decreased to 8 ng/mL. The post-therapeutic ^{131}I whole-body image showed iodine-avid bone metastases (Table 1).

Case 3: After TTE and neck lymph node dissection, a 68-year-old woman (No 3 in the Table 1) with histologically verified FTC underwent ^{18}F -FDG PET/CT, which showed higher uptake in multiple bone metastases (9th left posterior rib, Th11, Th12, L1 vertebrae with spinal cord compression, and left humerus) and multiple pulmonary metastases. The serum Tg level was 4581 ng/mL. Rapid regression of lung metastases and bone metastases with decreased Tg level to 4341 ng/mL were observed only three months after apatinib treatment. After one cycle of RAI therapy with 9.25 GBq (250 mCi) ^{131}I , Tg level decreased further to 2482 ng/mL. The post-therapeutic ^{131}I whole-body image showed positive bone metastases (Table 1).

Case 4: 11 years after TTE and neck lymph node dissection, a 51-year-old woman (No 4 in the Table 1) with FTC had an increasing serum Tg level of 74465 ng/mL. Positive ^{18}F -FDG PET/CT results were revealed in multiple mediastinal lymph nodes, bone (sternum, the 3rd and the 7th thoracic vertebra, the left 5th to 9th rib, bilateral iliac crest, and sacrum), pulmonary, liver and thoracic wall metastases (Fig. 3A, 3Aa and 3Ab). After 4 month treatment with Apatinib, the serum Tg decreased to 4439 ng/mL. ^{18}F -FDG PET/CT showed notable reduction in both ^{18}F -FDG uptake and tumour size of all metastatic lesions (Fig. 3B, 3Ba and 3Bb). However, three month after one cycle of RAI therapy with 9.25 GBq (250 mCi) ^{131}I , no further regression of metastases and reduction of metabolic activities were observed (Fig. 3C, 3Ca and 3Cb). Tg level was constant at 4700 ng/mL. All metastases were negative in the post-therapeutic ^{131}I whole-body image (Table 1).

Case 5: A 58-year-old woman (No 5 in the Table) suffered a lumbar pathological fracture with cold nodule in the thyroid and increased serum Tg level (20130 ng/mL). TTE was performed and histological examinations confirmed both FTC and papillary thyroid cancer (PTC) with bone metastases. ^{18}F -FDG PET/CT showed FDG-avid multiple bone metastases (Fig. 4A, 4Aa to 4Ad). Six months after apatinib therapy, the serum Tg increased to 24480 ng/mL and ^{18}F -FDG-PET/CT showed increased tumour size and SUVmax in right acetabulum with a new bone metastasis formation in right os ilium (Fig. 4B, 4Ba to 4Bd). RAI therapy with 7.4 GBq (200 mCi) ^{131}I was then performed. Post-therapeutic ^{131}I -whole body scan (WBS) showed uptake of ^{131}I in bone metastases. ^{18}F -FDG-PET/CT revealed a reduction in tumour size and SUVmax (Fig. 4C, 4Ca to 4Cd) as well as a decrease in Tg level to 9123 ng/mL in 3 months after the combination therapy with RAI and apatinib.

As shown in Table 1, statistically significant decreases in tumour size and SUVmax (both $p < 0.01$) were found in cases 1 to 4 after apatinib treatment compared with those before the apatinib therapy. Further significant reductions in tumour size and SUVmax (both $p < 0.01$) were demonstrated in cases 1, 2 and 3 after the combination therapy with RAI and apatinib compared with those after the apatinib therapy. The serum Tg levels showed remarkably reduced after apatinib therapy or after the combination with RAI, however, no statistical significance were observed due to the small numbers of patients.

The anti-Tg-antibody values in all patients before and after therapy were under the reference range (≤ 4.11 IU/ml).

Positive post-therapeutic ^{131}I whole-body images were shown in cases 1, 2, 3 and 5. All metastases were negative in the post-therapeutic ^{131}I whole-body image in case 4.

All patients suffered from grade 1 to 3 apatinib treatment-related adverse events, most of them were grade 1 to 2. There were no severe adverse events during and after treatment with apatinib.

Discussion

Apatinib is an orally anti-angiogenic TKI targeting VEGFR2 and PDGFR β [6] and has been approved by the National Medical Products Administration (NMPA) for advanced gastric cancer as third-line systemic therapy [10]. Recently, apatinib has been shown to be a promising treatment option for progressive locally advanced or metastatic RAI-DTC [7, 8]. Here, we reported the beneficial antitumour effects of apatinib alone or in combination with RAI therapy on progressive dmDTC. To the best of our knowledge, this is the first investigation into the neoadjuvant therapy effects of apatinib and the combination therapy with RAI on progressive dmDTC. Our results suggested that apatinib induced significant decrease in tumour size in patients with aggressive dmDTC. Apatinib alone has antitumour effect and beneficial synergistic and complementary effects were shown when apatinib combined with RAI therapy in the treatment of dmDTC.

Patients with dmDTC usually have an unfavorable prognosis, because some of dmDTC are RAI-DTC [2, 3]. TKIs such as lenvatinib and sorafenib have been approved by FDA and European Medicine Agency (EMA) for progressive, metastatic RAI-DTC [4, 5]. However, the therapy options for RAI-DTC patients in China are still very limited due to limited availability of lenvatinib and sorafenib. TKI has been reported as a successful neoadjuvant for total thyroidectomy to reduce tumor burden [11] and enhance RAI sensitivity of thyroid cancer including an increased sodium/iodide symporter expression [12]. ^{18}F -FDG PET/CT has been widely used in the diagnosis of mDTC and ^{18}F -FDG-avid lesions are usually more aggressive with poor prognosis [13, 14]. Previous studies have shown less effective of high-dose RAI therapy in patients with FDG-avid DTC than in patients with non-FDG-avid DTC [14] and there is an inverse relationship between RAI and ^{18}F -FDG accumulation in DTC cells [15]. In our present study, all patients have ^{18}F -FDG-avid dmDTC lesions suggesting aggressive diseases and less effective RAI therapy. We therefore explore the use of neoadjuvant treatment with apatinib prior to RAI therapy for evaluation of effect of apatinib on tumour progression and possible improvement of following RAI treatment results. Our present study demonstrated interestingly the effective treatment of apatinib on progressive dmDTC as shown in cases 1, 2, 3 and 4. Further synergistic antitumour effects were found in combination with apatinib and RAI therapy in cases 1, 2 and 3 by showing further decrease in tumour size and SUVmax as well as serum Tg level. In case 4 the patient was effectively treated by apatinib, however, RAI therapy showed no effect on the dmDTC, since all metastatic lesions in this case were negative in post therapeutic ^{131}I scan, these metastatic lesions may be defined as RAI-DTC. The reasons why the patient in case 5 showed no response to apatinib remain unclear. In contrast to other four patients with FTC in cases 1 to 4, this patient had both FTC and PTC. It is well known that DTC may have heterogeneous response to TKIs [16].

Apatinib suppresses tumour progression via blocking the VEGFR2 cascade in malignant cells [6]. Unfortunately, the tumour tissue VEGFR2 status in this case was unknown. We can only speculate that the tumour progression in this case might be through other molecular pathways rather than VEGFR2 pathway. Fortunately, this patient had response to RAI therapy leading to stable disease (SD) after RAI therapy. It might be possible that the positive effect of RAI on the metastatic lesions in case 5 might be partly due to the apatinib therapy since TKI may enhance the RAI sensitivity of thyroid cancer [12]. Our results may have implication for the complementary effect of combination therapy with apatinib and RAI as shown in cases 4 and 5.

Despite the small number of patients, our results demonstrated statistically significant reduction of tumour size and SUVmax under apatinib therapy indicating the clinical potential of apatinib therapy. Further significant decrease in tumour size and SUVmax demonstrated the synergistic and complementary effects of the combination of RAI with apatinib. The serum Tg levels which may indicate the tumour activity showed remarkably reduced after apatinib therapy and after the combination therapy with RAI, however, no statistical significance were observed due to the small numbers of patients.

There were some limitations in this study. Firstly, the number of investigated cases was limited. Secondly, there was no control group. The present study was a pilot study to evaluate the effects of apatinib on progressive dmDTC. More patients should be included in a randomized study to verify the results. Meanwhile, all patients are still alive.

In conclusion, apatinib is effective to inhibit the tumour progression of dmDTC. Furthermore, apatinib combined with RAI therapy might have beneficial synergistic or complementary antitumour effect on progressive dmDTC.

Declarations

Ethical approval:

All procedures performed in studies involving human participants were approved by the Institutional Review Board of Nanjing First Hospital and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate and for publication:

Informed consent was obtained from all patients.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing interests:

The authors declare to have no competing interests

Funding:

This work was supported by grants from the National Natural Science Foundation of China (11805104, 82003532, 82001865), the National Thyroid Research Project for Chinese Young and Middle-aged Doctors (2020), the Clinical Research Project of Nanjing Medical University (NMUB2019169), the Natural Science Foundation of Jiangsu Province (BK20200145), Jiangsu Provincial Key Research and Development Special Fund (BE2017612), Nanjing Medical Foundation (ZKX17027), the Health Commission of Jiangsu Province (H2019091), Nanjing Medical and Health International Joint Research and Development Project (201911042), the Second Round Fund of Nanjing Clinical Medical Center "Nanjing Nuclear Medicine Centre",

Authors' Contributions:

Feng Wang, Yan-song Lin, and Shuren Li conceived and designed the study. Feng Wang, Liang Shi and Shaohua Li supervised the study. Jun Wang and Qinqin You did the statistical analysis. Liang Shi, Shaohua Li, Hanjin Wang, Rui Tian, Xiaochen Yao, and Lele Zhang, Wenyu Wu contributed to acquisition, analysis, and interpretation of data. Feng Wang, Yan-song Lin, Liang Shi and Shuren Li drafted the manuscript.

Acknowledgements:

We thank the thyroid cancer multidisciplinary discussion team of thyroid cancer rapidat Nanjing First Hospital, Dr. Yue Huang, Dr. Yuan Fang, and Dr. Muhong Guo, for their valuable treatment suggestions for the selection of treatment. We also thank Dr. Susan Furness from Liwen Bianji (Edanz) (www.liwenbianji.cn/) for valuable suggestion for the English text of this manuscript. This study was partly supported by the Scientific & Technological Cooperation with China Project No. CN 06/2020 of Austrian Agency for International Cooperation in Education and Research (OEAD), and the Federal Minister of Education, Science and Research (BMBWF), Austria.

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Figures

Figure 1

Figure 1

Patient flow diagram.

Figure 2

Figure 2

In case 1, ^{18}F -FDG PET/CT showed dmDTC before apatinib therapy (A, Aa, Ab, Ca and Cb). Decreased tumour sizes and SUVmax in the right 10th rib (red arrows) and in the left acetabulum (orange arrows) after neoadjuvant therapy with apatinib for 4 months (B, Ba, Bb, Da and Db) and further decrease in tumour size in the left acetabulum after apatinib combined with RAI (Ea and Eb). Immunohistochemistry assay confirmed expression of VEGFR2 in the tumour tissue (Magnification, $\times 400$) (F).

Figure 3

Figure 3

In case 4, ^{18}F -FDG PET/CT revealed multiple mediastinal lymph nodes, pulmonary, liver and left 5th to 9th ribs as well as left thoracic wall metastases (A, Aa and Ab). Decreased tumour size and SUVmax after 4-month therapy with apatinib (B, Ba and Bb). However, no further decrease of tumour size was observed after apatinib therapy combined with RAI (C, Ca and Cb). Red arrows indicated metastases in left 5th to 9th ribs as well as left thoracic wall.

Figure 4

Figure 4

In case 5, ^{18}F -FDG PET/CT showed bone (right 5th rib and right acetabulum) metastases before apatinib therapy (A and Aa to Ad). Increased tumour sizes and a new metastasis formation in the right ilium were revealed after 6-month therapy with apatinib (B, Ba to Bd). After combined therapy with RAI, decreases in tumour sizes and SUVmax were shown (C, Ca to Cd). Red arrows indicated metastasis in the right 5th rib and orange arrows metastases in the right acetabulum.

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