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Clinical Effect Observation of Apatinib Combined with 131I for Radioiodine-Refractory Differentiated Thyroid Cancer and Prognostic Significance Analysis of Macrophage Inflammatory Protein-1α After Treatment: A Cell Regulation Study

Observación del Efecto Clínico de Apatinib Combinado con 131I para el Cáncer de Tiroides Diferenciado Resistente al Yodo Radiactivo y Análisis de Importancia Pronóstica de la Proteína Inflamatoria 1α de Macrófagos Después del Tratamiento: Un Estudio de Regulación Celular

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LIU, J.; LI, M.; ZHENG, W. & WANG, M. Clinical effect observation of apatinib combined with 131I for radioiodine-refractory differentiated thyroid cancer and prognostic significance analysis of macrophage inflammatory protein-1α after treatment: A cell regulation study. *Int. J. Morphol., 42(2)*:409-415, 2024.

SUMMARY: The objective of this study was to observe the clinical efficacy of apatinib (AP) combined with 131I in the treatment of radioiodine-refractory differentiated thyroid cancer (RAIR-DTC) and the prognostic significance of MIP-1α after treatment, and to provide reference and guidance for future treatment and disease assessment of RAIR-DTC. One hundred and six patients with RAIR-DTC admitted to our hospital from January 2019 to October 2020 were selected for the study. All the patients were treated with TC surgery with 131I at our hospital, and 58 of them were subsequently transferred to AP treatment, which was considered as the research group; the other 48 patients were transferred to thyroid stimulating hormone (TSH) suppression treatment, which was considered as the control group. The clinical efficacy of the research group was better than that of the control group ($P < 0.05$), while no difference was seen in the comparison of the incidence of adverse effects and thyroid function ($P > 0.05$). After treatment, Tg, TL, maximum diameter of C/B lymph nodes, number of lymph nodes and number of calcified spots were lower in the research group than in the control group ($P < 0.05$). ROC analysis revealed that the predictive sensitivity of MIP-1α for prognosis of 3-year RAIR-DTC death in the research group of patients was 84.63 % and the specificity was 72.16 %. AP combined with 131I is effective in the treatment of RAIR-DTC and is worth using in the clinical practice. In addition, elevated levels of MIP-1α predicted a poor prognosis for patients with RAIR-DTC.

KEY WORDS: Apatinib; 131I; Radioiodine-refractory differentiated thyroid cancer; MIP-1α; Clinical efficacy.

INTRODUCTION

The thyroid gland is an endocrine gland located anterior to the subglottic node and consists of two lateral lobes, the right and left, and the isthmus, which secretes hormones to control the metabolic homeostasis of the body. Thyroid carcinoma (TC) is a change in the biological nature of some tissues of the thyroid gland and is the most common malignancy of the head and neck. The incidence of TC has been growing rapidly worldwide in recent years, among which China is continuing to grow at an average annual rate of 20 % due to its large population base, and the incidence is significantly higher in women than in men. Some data show that the disease is expected to become the fourth leading cancer worldwide (Ibrahimpasic *et al*., 2019). TC is composed of several carcinomas with different biological behavior as well as different pathological types, such as papillary carcinoma and differentiated thyroid cancer (DTC). Of these, DTC is the most common, accounting for approximately 85-95 % of all TCs (Oh & Ahn, 2021). Such patients can lose their ability to ingest iodine as the disease progresses, and approximately 5-23 % will eventually develop radioiodine-refractory DTC (RAIR-DTC) (Liu *et al*., 2019). As for refractory RAIR-DTC, which is the most malignant category of TC, the prognosis of patients is extremely bleak, with a prognosis of less than 10 % survival at 10 years (Brose *et al*., 2021). Therefore, the exploration of treatment options for RAIR-DTC has been a hot and difficult research topic clinically.

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Iodine-131 (131I) is the main clinical treatment for conventional TC, but since patients with RAIR-DTC have lesions that do not uptake iodine, termination of 131I to other treatment options such as TSH suppression therapy, extracorporeal radiotherapy, and radiofrequency ablation can usually be considered at this time (Brose *et al*., 2022). However, none of these options are effective and patients may still be at greater risk of disease progression (Wirth *et al*., 2022). Apatinib, a small molecule vascular endothelial growth factor receptor 2 tyrosinase inhibitor that inhibits tumor angiogenesis and enhances immunity, is a targeted drug developed independently by China. In a phase II clinical trial for RAIR-DTC, AP has been shown to be effective in shrinking tumor lesions in patients with an objective remission rate of 80 % (Lin *et al*., 2022).

Therefore, in order to further confirm the results of AP in RAIR-DTC, we will explore the clinical effect of AP combined with 131I in the treatment of RAIR-DTC and analyze the prognostic significance of MIП−1α after treatment to provide effective guidance, reference basis for the future clinical treatment.

MATERIAL AND METHOD

Patient collection. One hundred and six patients with RAIR-DTC admitted to our hospital from January 2019 to October 2020 were selected as study subjects. All patients received TC surgery with 131I at our hospital, and 58 patients were subsequently transferred to AP treatment and considered as the research group; the other 48 were converted to TSH suppression treatment and considered as control group. The experiment was conducted with the consent of our ethics committee and met the criteria in the Declaration of Helsinki (World Medical Association, 2013). All patients signed the informed consent form.

Patient inclusion criteria. Inclusion criteria: the diagnosis of TC was confirmed by pathology department biopsy (Haddad *et al*., 2022) and relevant treatment was performed in our hospital. Complete (progressive/partial) loss of iodine uptake ability of the lesion was found after 131I treatment or (and) metastatic progression after 131 treatment, and DRAIR-DTC was diagnosed and treated accordingly. Patient information is complete, and cooperation is high. Exclusion criteria: coagulation disorders; major organ failure and dysfunction; lactating and pregnant women; those combined with serious infectious disease; transferred, died, or withdrawn from the study; positive thyroglobulin antibody (TgAb); those combined with serious underlying disease; combination of AIDS, syphilis, and other diseases; anemia and immunocompromised; combination of other thyroid diseases.

Treatment methods. After admission, the patients were all treated by the same surgical team in our hospital to complete TC radical surgery and were treated with 131I radiation therapy (Chengdu Zhonghe Gaotong Isotope Co., Ltd., SFDA Approval No. H10983121) with 100 mCi taken on an empty stomach.After confirmation of RAIR-DTC, the research group was given AP (Jiangsu Hengrui Pharmaceutical Co., Ltd., SFDA Approval No. H20140104): 500 mg, 1 time/d, half an hour after meals (the same daily dosing time as possible), while patients were closely monitored for adverse effects and adjusted as needed to enable patients to tolerate the treatment. The control group was given levothyroxine sodium tablets (Merck KGaA, SFDA Approval No. H20140052) at an initial dose of 50 μg/d orally in the early morning, and the dose was adjusted to 100 μg/d after 2 weeks of continuous treatment. The TSH level is 0.05-0.10 mIU/L. The dosage of the drug is adjusted according to the patient's TSH level during the treatment. If the patient develops hyperthyroidism, the medication needs to be stopped immediately.

Outcome measures. After 2 months of treatment, the clinical outcomes of the two groups were compared with reference to the Response Evaluation Criteria in Solid Tumors (Wang *et al*., 2011). Complete remission (CR): complete disappearance of the lesion; partial remission (PR): reduction in the size of the lesion by > 50 % compared to the original lesion and lasting for more than 3 months; stable disease (SD): 0 % to 50 % reduction in lesion volume; progressive disease (PD): no reduction in lesion volume and increasing; disease control rate (DCR) = (CR + PR + SD) / total number of cases × 100 %. Comparison of thyroid function between the two groups before and after treatment: venous blood was drawn from both groups before and after treatment, and thyrotropin, free thyroxine (FT4) and free triiodothyronine (FT3) were measured by automatic immunoassay analyzer. The levels of thyroglobulin (Tg), thyroglobulin antibody (TgAb) and protein kinase B (AKT) were measured by enzyme-linked immunoluminescence analyzer, and the maximum diameter of lymph nodes, the number of lymph nodes and calcification points were observed by ultrasonography. All patients were scanned by whole-body SPECT, and the radioactivity counts of the concentrated 131 I foci were quantified and analyzed using the method of radioactivity count comparison, i.e., 131 I concentrated radioactivity count/background count (Concentration range count/background count, C/B) of the target lesion to determine the treatment effect. Adverse effects during treatment were also counted. After treatment, fasting venous blood was drawn from patients in the research group and MIP-1α levels were measured by ELISA. Patients in the research group were followed up

for 1 year prognostically, and prognosis death was recorded to analyze the relationship between MIP-1a on the prognosis of RAIR-DTC patients after AP combined with 131I treatment.

Statistical methods. SPSS 25.0 software was used for statistical analysis. The counting data [n (%)] were compared by the χ^2 test, and the independent-sample t test was used for all comparisons of measurement data ($\bar{\chi} \pm s$). Pre- and post-treatment comparisons were performed using paired t-tests, and predicted effects were analyzed using ROC. A P value of < 0.05 for the results of statistical analysis indicated that the difference between groups was statistically significant.

RESULTS

Patient baseline data. Comparison of baseline data such as age, BMI, sex, family history of disease, and smoking or not between the two groups showed no statistical difference between the two data groups (P > 0.05) (Table I).

Clinical efficacy of two groups of patients. The treatment efficacy of the two groups was counted and analyzed, and the results showed that the disease control rate of patients in the research group (94.83 %) was significantly higher than that of those in the control group (81.25 %), and the difference was statistically significant (P < 0.05) (Table II).

Thyroid function before and after treatment in both groups. Before treatment, there was no statistically significant difference (P > 0.05) in the comparison of FT4, FT3, and TSH between the two groups. While after treatment, FT4 and FT3 were lower in both groups compared with those before treatment, while TSH was higher (Figure 1).

Serological marker proteins before and after treatment in both groups. Similarly, the results of Tg, TgAb, and AKT assays were not significantly different between the two groups before treatment (P > 0.05). All three indexes were significantly lower after treatment, with Tg, TgAb, and AKT being lower in the research group than in the control group after treatment (P < 0.05) (Fig. 2).

Table I. Table of clinical baseline information.

Group	n	Age	BMI (kg/m^2)	Sex		Family history of disease		Smoking	
				Female	Male	Yes	No	Yes	No
Control group	48	50.10±3.72	23.84±1.70	34 (70.83)	14 (29.17)	5 (10.42)	43 (89.58)	18 (37.50)	30 (69.50)
Research group	58	49.47±3.20	23.96±1.56	42 (72.41)	16 (27.59)	5 (8.62)	53 (91.38)	25 (43.10)	33 (56.90)
t (χ^2)		0.951	0.393	0.032		0.099		0.342	
P		0.344	0.695	0.857		0.753		0.559	

Table II. Clinical efficacy.

Group	n	CR	PR	SD	PD	DCR
Control group	48	5 (10.42)	21 (43.75)	13 (27.08)	9 (18.75)	94.83
Research group	58	15 (25.86)	28 (48.28)	12 (20.69)	3 (5.17)	81.25
χ^2						4.823
P						0.028

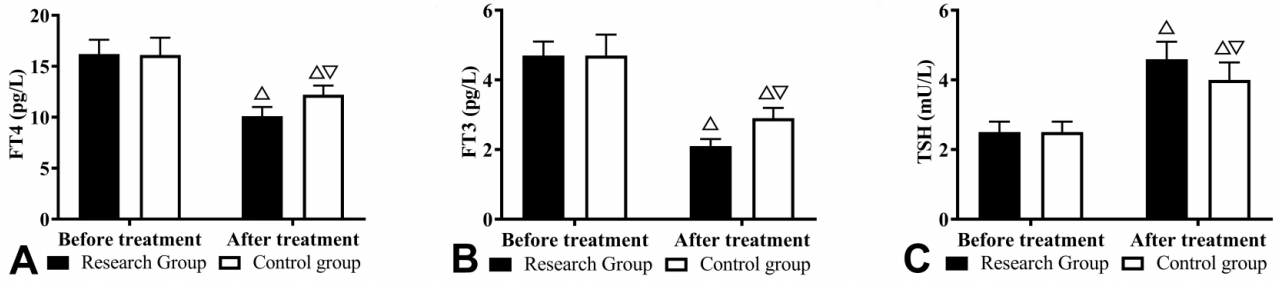

Fig. 1. Thyroid function before and after treatment. A) Comparison of FT4. B) Comparison of FT3. C) Comparison of TSH. Δ indicates a statistically significant difference from before treatment (P < 0.05), ∇ indicates a statistically significant difference with the research group (P < 0.05).

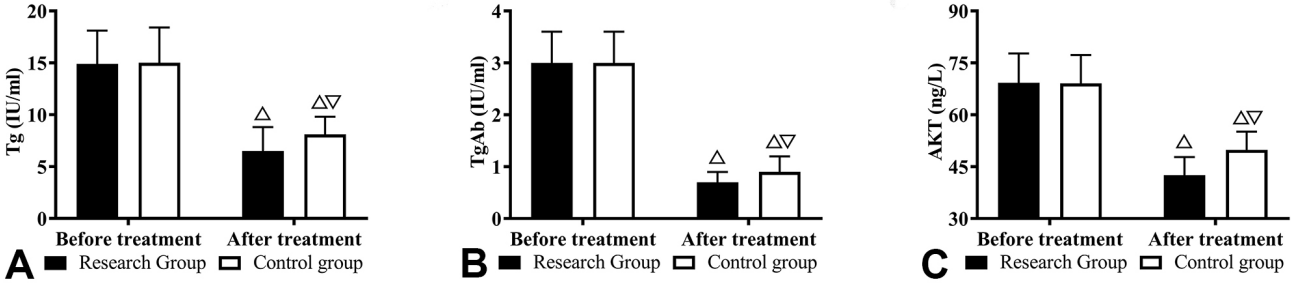

Fig. 2. Serological marker proteins before and after treatment. A) Comparison of Tg. B) Comparison of TgAb. C) Comparison of AKT. Δ indicates a statistically significant difference from before treatment ($P < 0.05$), ∇ indicates a statistically significant difference with the research group ($P < 0.05$).

Ultrasound findings in both groups. Ultrasound results showed that the maximum diameter of lymph nodes, and the number of lymph nodes and calcified spots were also lower in both groups after treatment, but the maximum diameter of lymph nodes, and the number of lymph nodes and calcified spots were lower in the research group than in the control group after treatment ($P < 0.05$) (Fig. 3).

Comparative analysis of C/B between two groups of patients. Both groups underwent whole-body SPECT scans after treatment. It was found that the C/B values in the research group were lower than those in the control group, indicating a significant reduction in lesion size in the research group, and the difference between the two groups was statistically significant ($P < 0.05$) (Fig. 4).

Incidence of adverse reactions during treatment in both groups. The adverse reactions occurred during the treatment period in both groups were counted andanalyzed, and the results showed that the incidence of total adverse reactions was 17.24 % in the research group and 16.67 % in the control group, and there was no statistical difference between the data of the two groups ($P > 0.05$) (Table III).

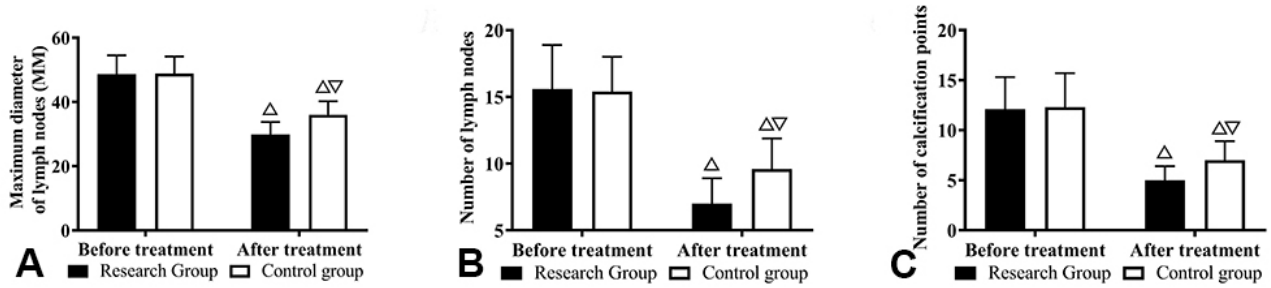

Fig. 3. Ultrasound findings in both groups. A) Comparison of maximum diameter of lymph nodes. B) Comparison of number of lymph nodes. C) Comparison of number of calcified spots. Δ indicates a statistically significant difference from before treatment ($P < 0.05$), ∇ indicates a statistically significant difference with the research group ($P < 0.05$).

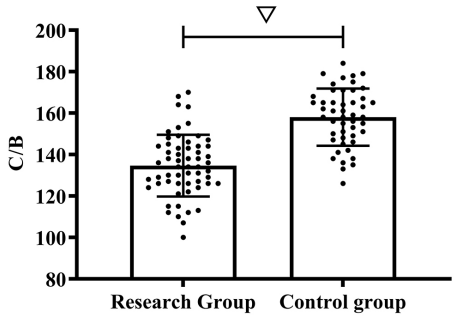

Fig. 4. Comparison of C/B after treatment. ∇ indicates $P < 0.05$.

Relationship between MIP-1a levels and prognosis of patients with RAIR-DTC. Finally, we looked at MIP-1α levels and the prognosis of patients with RAIR-DTC. In the prognostic follow-up, we successfully followed all patients in the research group, 8 of whom died, with an overall mortality rate of 13.79 %. The comparison showed that MIP-1α was significantly higher in deceased patients than in surviving patients after treatment ($P < 0.05$). ROC analysis showed a sensitivity of 75.00 % and specificity of 70.00 % ($P < 0.05$) for predicting prognostic death in patients with RAIR-DTC when post-treatment MIP-1α was > 18.30 pg/mL (Fig. 5).

Table III. Adverse effects during treatment.

Group	n	Abdominal pain and diarrhea	Loss of appetite	High blood pressure	Skin rash	Laryngitis	Total adverse reactions
Control group	48	3 (6.25)	1 (2.08)	1 (2.08)	2 (4.17)	1 (2.08)	16.67
Research group	58	4 (6.90)	3 (5.17)	0 (0.0)	1 (1.72)	2 (3.45)	17.24
χ^2							0.006
P							0.938

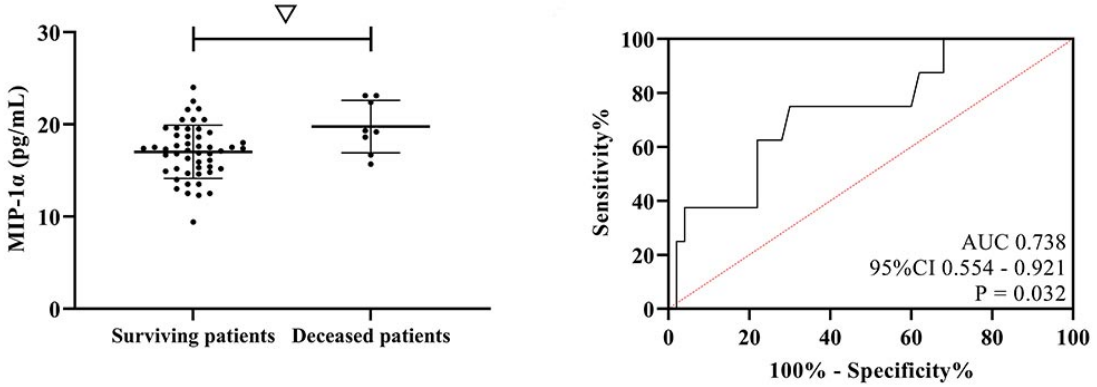

Fig. 5. Relationship between MIP-1α levels and prognosis of patients with RAIR-DTC. A) Comparison of MIP-1α in patients with prognostic death and surviving patients. B) ROC curve of MIP-1α predicting prognostic death in patients. ∇ indicates $P < 0.05$.

DISCUSSION

The incidence of TC, an extremely common clinical condition nowadays, has been increasing in recent years (Zou *et al*., 2021). 131I is currently the most common means of TC treatment, but during multiple 131I treatments, some lesions develop therapeutic resistance to 131I and transform into iodine-refractory RAIR-DTC (Singh *et al*., 2021). It is difficult for such patients to achieve biochemical remission and local target lesion remission, which eventually leads to disease progression and causes patient death (Yi *et al*., 2017). Therefore, finding an effective solution to this problem is important to improve the prognosis of RAIR-DTC patients in the future.

Recently, as several tyrosine kinase inhibitors (TKI) drugs have been introduced, these targeted agents have been shown in clinical trials to prolong progression-free survival (PFS) to varying degrees in patients with iodine-refractory RAIR-DTC (Scott, 2018). Among them, AP, a novel small molecule TKI drug, mainly acts on VEGFR-2 (Zhao *et al*., 2021). It is well known that VEGF and VEGFR play an important regulatory role in neovascularization, and the highly selective blockade of VEGFR-2 and its downstream signaling pathways by AP is utilized to inhibit the proliferation and migration of vascular endothelial cells to achieve tumor suppression (Zhang *et al*., 2022). Therefore, the combination of 131I through AP may effectively address the shortcomings of the current stage of 131I during the treatment of RAIR-DTC and provide more reliable prognosis for patients. The present study provides a reliable theoretical basis for future clinical use in the treatment of RAIR-DTC by investigating the effects of 131I combined with AP.

The results of this trial denoted no significant difference in thyroid function between the two groups after treatment, but the clinical efficacy of patients in the research group was better than that of the control group only, suggesting that the combination of AP can enhance the therapeutic effect of RAIR-DTC. And Li J *et al*., showed the same, which can corroborate our experimental results (Li *et al*., 2022). We speculate that this is mainly due to the good anti-angiogenic effect of AP, which inhibits the growth process of cancer tumor cells, reduces the damaging effect of cancer cells on thyroid tissue, and allows the normalization of thyroid tissue function and thus the normalization of all hormone levels. Not only that, the serum marker protein level of the patients treated in the research group was also better than that of the control group, which also confirmed the good therapeutic effect of AP on RAIR-DTC from the molecular biology point of view. It was found that AP not only inhibits the growth of cancer tumor cells by suppressing the activity of proto-oncogene-related proteins such as tyrosine protein kinase receptor and serine/threonine protein kinase B

associated with tumor cell proliferation, but also regulates the state of the tumor microenvironment in patients and can inhibit the expression of tumor microenvironment-associated proteins. We speculate that this is the main reason for the more desirable improvement of RAIR-DTC serum marker protein in the research group, but of course, the exact mechanism still needs to be confirmed by further studies. This study found that the research group also had a more significant reduction in C/B after treatment than the control group, which further indicates that AP can maximize the killing of tumor cells and save the lives of RAIR-DTC patients. Moreover, we also found no significant difference in the adverse reactions during treatment between the two groups, which supports the high safety of AP use and its high clinical use value.

On the other hand, there is still a lack of reliable and rapid evaluation indexes for the assessment of RAIR-DTC, which also greatly contributes to the recurrence of RAIR-DTC or even death in some patients after treatment. To address this situation, we sought to assess the prognosis of patients with RAIR-DTC by MIP-1α. And the results of the study showed that MIP-1α levels were significantly higher in patients who died prognostically than in those who did not, and that MIP-1α demonstrated excellent prediction of prognostic death in patients with RAIR-DTC. It is known that MIP-1α is an important chemokine in humans that promotes the aggregation of T lymphocytes at the site of inflammation and can also chemotactic some immune cells such as natural killer cells and monocytes into the site of inflammation (Ntanasis-Stathopoulos *et al*., 2020). Some clinical studies have shown that the expression levels of MIP-1α in the serum of patients with various malignancies, such as liver cancer and breast cancer, are significantly higher than those in the healthy population, which fully confirms the close relationship between MIP-1α and the development of malignancies (Ahmad *et al*., 2019). We hypothesized that in patients with prognostic death from RAIR-DTC, MIP-1α could chemotactic monocytes and activated macrophages, and the release of large amounts of lysozyme would severely compromise the immune function of patients. In contrast, tumors, as products of malignant transformation of normal cells, also express some antigens that are not expressed by normal cells, and the body's immune system will activate the immune response after recognizing tumor antigens (Kim *et al*., 2017). As a broad immune disease, the metastasis and spread of malignancies caused elevated levels of MIP-1α expression in patients. Based on the above experimental results, we can rapidly assess the prognosis of patients by monitoring their post-treatment MIP-1α levels and promptly formulate targeted interventions to ensure their prognosis for recovery.

Nevertheless, there are still many weaknesses in this study that could be improved, such as the small number of cases included and the short follow-up period, which may have biased the results. Subsequently, we need to increase the number of cases and conduct randomized controlled trials for confirmation. Meanwhile, we also need to carry out *in vitro* experiments to confirm the specific mechanism of the effect of AP on RAIR-DTC and further analyze the role of MIP-1α in RAIR-DTC to provide a more reliable reference for clinical practice.

CONCLUSION

AP combined with 131I is effective and has a high safety profile in the treatment of RAIR-DTC, which can effectively inhibit the progression of RAIR-DTC and is expected to become a new option for the treatment of RAIR-DTC. MIP-1α can effectively assess the prognosis of death in RAIR-DTC. In the future, the clinic can quickly assess the prognosis of RAIR-DTC patients and formulate timely countermeasures to provide a more reliable safety guarantee for the prognosis of patients.

LIU, J.; LI, M.; ZHENG, W. & WANG, M. Observación del efecto clínico de apatinib combinado con 131I para el cáncer de tiroides diferenciado resistente al yodo radiactivo y análisis de importancia pronóstica de la proteína inflamatoria 1α de macrófagos después del tratamiento: Un estudio de regulación celular. *Int. J. Morphol., 42(2)*:409-415, 2024.

RESUMEN: El objetivo de este estudio fue observar la eficacia clínica de apatinib (AP) combinado con 131I en el tratamiento del cáncer de tiroides diferenciado refractario al yodo radiactivo (RAIR-DTC) y la importancia pronóstica de MIP-1α después del tratamiento, y proporcionar referencia y orientación para futuros tratamientos y enfermedades. Evaluación de RAIR-DTC. Se seleccionaron para el estudio 106 pacientes con RAIR-DTC ingresados en nuestro hospital desde enero de 2019 hasta octubre de 2020. Todos los pacientes fueron tratados con cirugía CT con 131I, y 58 de ellos fueron trasladados posteriormente a tratamiento AP, los que fueron considerados como grupo de investigación; los otros 48 pacientes fueron transferidos a tratamiento de supresión de la hormona estimulante de la tiroides (TSH), que se consideró como grupo de control. La eficacia clínica del grupo de investigación fue mejor que la del grupo de control (P < 0,05), mientras que no se observaron diferencias en la comparación de la incidencia de efectos adversos y la función tiroidea (P > 0,05). Después del tratamiento, Tg, TL, diámetro máximo de los linfonodos C/B, número linfonodos y número de manchas calcificadas fueron menores en el grupo de investigación que en el grupo de control (P <0,05). El análisis ROC reveló que la sensibilidad predictiva de MIP-1α para el pronóstico de muerte por RAIR-DTC a 3 años en el grupo de pacientes de investigación fue del 84,63 % y la especificidad fue del 72,16 %. AP combinado con 131I es eficaz en el tratamiento del RAIR-DTC y vale la pena utilizarlo en la práctica clínica. Además, los niveles elevados de

MIP-1α predijeron un mal pronóstico para los pacientes con RAIR-DTC.

PALABRAS CLAVE: Apatinib; 131I; Cáncer de tiroides diferenciado refractario al yodo radiactivo; MIP-1α; Eficacia clínica.

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