37P: GROWTH/DIFFERENTIATION FACTOR-15 FROM BIOMARKER TO TARGET IN CANCER

Adina E. Stanciu[1], Lucica M. Bolovan[1], Alexandra M. Lazar[2], Mario D. Mutuleanu[2], Marcel M. Stanciu[5], Laurentia N. Gales[3], Anca Zamfirescu[4], Mirela Gherghe[2]

[1]Department of Carcinogenesis and Molecular Biology; [2] Department of Nuclear Medicine; [3]Department of Oncology; [3]Department of Radionuclide Therapy, Institute of Oncology Bucharest, Romania; [5]University Politehnica of Bucharest, Bucharest, Romania

Institutul Oncologic Prof.Dr. Alexandru Trestioreanu Bucuresti

Introduction

Growth and differentiation factor-15 (GDF-15) is a divergent member of the transforming growth factor β family associated with pathological conditions, including myocardial ischemia, autoimmune disease, and cancer. Studies on the role of GDF-15 in cancer are limited and controversial. Radioactive iodine (^{131}I) ablation of the post-surgical thyroid remnants, as an immunomodulatory tool, is the standard treatment for differentiated thyroid carcinomas. Given the aggressive nature of HER2-positive breast cancer, neoadjuvant dual anti-HER2 blockade (trastuzumab + pertuzumab) in combination with chemotherapy has been shown to improve clinical outcomes through immune system activation.

Aim

We hypothesized that the predictive value of GDF-15 as a biomarker in DTC with and without type 2 diabetes mellitus (DTC/+T2DM and DTC/−T2DM) and HER2-positive breast cancer might plausibly be linked to its immune-regulatory function.

Methods and Patients

DTC Group:

Subgroup 1: 56 patients with DTC/−T2DM (mean age 57.3±9.1 years)
Subgroup 2**:** 11 patients with DTC/+T2DM (mean age 61.6±7.8 years)

Peripheral blood samples were collected before and 4 days after ^{131}I administration for all DTC patients (DTC/−T2DM and DTC/+T2DM).

HER-2 positive breast cancer Group

Table 1. Patients Characteristics in the HER-2 Positive Breast Cancer Group

Patient Characteristic		Value
Age (mean ± SD)		55.55±9.89 years
Tumor grading	G2	45.5 %
	G3	54.5 %
PR	Positive	59.1 %
	Negative	40.9 %
ER	Positive	54.5 %
	Negative	45.5 %
HER2 status	2+	40.9 %
	3+	50.1 %
Metastatic disease	Yes	54.5 %
	No	45.5 %
Previous chemotherapy	Anthracyclines	40.9 %
	Taxanes	77.3 %

Peripheral blood samples were collected before and 6 months after neoadjuvant treatment. The serum levels of GDF-15 were measured by ELISA.

Results

Before Therapy

- ✓ GDF-15 concentration was higher in the HER- 2 positive breast cancer than in the DTC/−T2DM subgroup (1522.4 pg/mL vs. 915.02 pg/mL, P < 0.001).
- ✓ Regarding the DTC study group, the association of DTC with T2DM led to higher GDF-15 serum levels (P < 0.001).

After Therapy

- ✓ A modulation in GDF-15 level was measured in response to HER-2 inhibitors treatment (reduction by 18.8%). Between the baseline and the follow-up time, patients underwent a treatment regimen that included an initial administration of trastuzumab 8 mg/kg, pertuzumab 840 mg, and docetaxel 75 mg/m^2, followed by a regimen compounded of trastuzumab 6 mg/kg, pertuzumab 420 mg and docetaxel 100 mg/m^2, administered through intravenous infusion every 21 days, for at least 7(±1) cycles.
- ✓ In the DTC/−T2DM and DTC/+T2DM study subgroups, the ^{131}I effect was illustrated by a GDF-15 significant increase (97.9% and 169.8%, respectively) in a dose-dependent fashion (Table 2)

The rate of change was defined as the ratio between the variable measured at time T0p and the baseline value (T0i). These new variables are dimensionless quantities, expressed by number one.

Table 2 Rates of change for each measured biomarkers in the two group

Patients	GDF15	
	T0i	T0p
DTC Group		
Subgroup 1 (DTC/−T2DM)	1.00	1.97
Subgroup 2 (DTC/+T2DM)	1.00	2.69
HER2-positive breast cancer Group	1.00	0.81

Subgroup 1 – DTC/−T2DM (Differentiated Thyroid Carcinoma − Type 2 Diabetes Mellitus)
Subgroup 2 – DTC/+T2DM (Differentiated Thyroid Carcinoma + Type 2 Diabetes Mellitus)
T0i – baseline (before ^{131}I therapy for DTC Group; before neoadjuvant therapy for HER-2 positive breast cancer Group)
T0p – 4 days after ^{131}I therapy for DTC Group; after 6 months of treatment with trastuzumab + pertuzumab + docetaxel for HER-2 positive breast cancer Group

The 18.8% decrease in serum GDF-15 concentration after 6 months of treatment with trastuzumab, pertuzumab, and docetaxel might have come as a response to the therapeutic scheme.

In the DTC/−T2DM subgroup, the increase in the GDF-15 serum level was positively correlated with the cumulative dose of ^{131}I at follow-up (r=0.68, P<0.001) as shown in Figure 1.

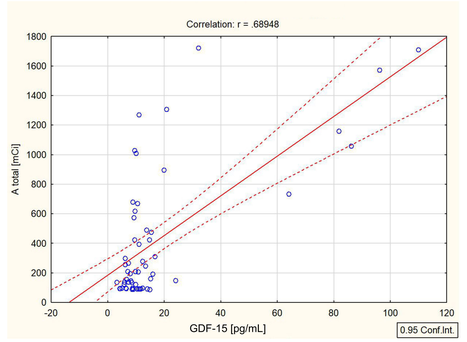

Fig. 1. *Correlation between GDF-15 and cumulative dose of ^{131}I in DTC/−T2DM subgroup.*

Conclusions

- ➢ The described associations and mechanistic data suggest that GDF-15 might be a radiation-induced early biomarker in DTC female patients (DTC/−T2DM and DTC/+T2DM subgroups) .
- ➢ Furthermore, GDF-15 may act as a biomarker of response to action and synergism of trastuzumab and pertuzumab in targeting HER2-positive breast cancer.
- ➢ With a better understanding of the upstream cancer pathways reflected by GDF-15, new treatment targets may emerge.

References

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For more information:
Email: adinaelenastanciu@yahoo.com