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PROGNOSTIC SIGNIFICANCE OF TGF-B-ASSOCIATED PROTEINS IN BREAST CANCER PATIENTS TREATED WITH ADJUVANT TAMOXIFEN

T.A. Dronova[1,2], N.N. Babyshkina[1,2], S.V. Patalyak[1], N.V. Cherdyntseva[1,2]

Cancer Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia[1]
Tomsk State University, Tomsk, Russia[2]

We investigated the effect of 3 TGF-β-associated signaling components (TGF-β1, TGF-βR1, TGF-βR2) and ERα on the response to adjuvant tamoxifen treatment in 122 estrogen positive breast cancer patients. Our data suggest that the gene and protein expression of TGF-βR1 as well as *ESR1* rs2228480 and the distribution pattern of ERα expression may play a significant role in the development of tamoxifen resistance/sensitive in breast cancer patients.

Introduction

Crosstalk between ERα and TGF-β signaling may be critical in the development of tamoxifen resistance/sensitive in breast cancer. It is well known that ERα blocks TGF-β pathway by direct interactions with Smads components [1]. In turn to, TGF-β could act to restrict ERα-mediated proliferation [2]. While evidence is accruing that TGF-β-associated proteins is implicated in the tamoxifen resistance, there have been no integrated studies evaluating their prognostic value in estrogen positive breast cancer patients.

This has prompted us to assess the genetic variation, protein and RNA expressions of the three TGF-β-associated signaling components (TGF-β1, TGF-βR1, TGF-βR2) and ERα in relation to tamoxifen efficacy and survival rate in estrogen positive breast cancer patients.

Material and Methods

This study analyzed clinical data and tissue samples from 122 women with breast cancer who received adjuvant tamoxifen at the Tomsk National Research Medical Center from 2002 to 2014. According to the response to tamoxifen, all patients were divided into tamoxifen resistance (TR) group and tamoxifen sensitive (TS) group. The TGF-βR1rs334354, TGF-βR2rs2228048 and ESR1 (rs2228480, rs2077647, rs1801132, rs3798577) SNPs were analysed using a TaqMan assay. Expression of the TGF-β1, TGF-RI, TGF-RII and ESR1 gene was detected by RT-PCR analysis. Expression of TGF-βRI and the distribution pattern of ERα expression were assessed by immunohistochemistry. Progression-free survival (PFS) was analyzed by Kaplan-Meier curves. SPSS 21.0 (IBM SPSS Statistics, Armonk, NY, USA) was applied for statistical analysis.

Results

When primary tumors from the tamoxifen resistance and tamoxifen sensitive groups were compared, *TGF-βRI* mRNA was significantly overexpressed in the latter group (p=0.041). Furthermore, we demonstrated that TGF-βR1 positive protein expression was more frequent in tamoxifen sensitive tumors as compared to tamoxifen resistance (p=0.030). We found that the wild genotype of the *TGF-βR2*rs2228048 was significantly associated with sensitivity to tamoxifen treatment in breast cancer patients when compared with the mutant and heterozygous genotypes (p=0.045).

We noted a significant association between low mRNA *ESR1* expression and resistance to tamoxifen (p=0.041). Patients carrying a mutant genotype of the *ESR1*rs2228480 had a high of progression risk after tamoxifen treatment than the patients with a wild and heterozygous genotypes (p = 0.013). In addition, we were able to demonstrate that heterogeneous ERa expression was significantly associated with tamoxifen resistance (p = 0.003).

We assessed the association of all studied markers with progression-free survival rate in breast cancer patients. Compared with TGF-βR1-posinive patients, TGF-βR1-negative patients showed significantly poorer outcomes with respect to progression-free survival (p=0.032). Kaplan-Meier analysis showed that there were significant higher death and recurrence risk in patients with heterogeneous ERa expression and mutant genotype of rs2228480 SNP compared with those patients with homogeneous ERa expression pattern and wild and heterozygous genotypes of rs2228480 SNP (p=0.009 and p=0.040, respectively).

Conclusion

Our data suggest that the gene and protein expression of TGF-βR1 as well as *ESR1* rs2228480 and the distribution pattern of ERα expression may play a significant role in the development of tamoxifen resistance/sensitive in breast cancer patients.

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ANALYSIS OF THE LEVEL OF THE SERUM TUMOR MARKERS AND CHEMICALS IN WATERBASINS OF THE REPUBLIC OF SAKHA (YAKUTIA)

S.D. Efremova[1], A.S. Golderova[1], V.M. Nikolaev[1], E.D. Okhlopkova[1], V.A. Alekseev[1], F.V. Vinokurova[1], E.K. Rumyantsev[1], E.V. Tsypandina[1]

Scientific Center of Complex Medical Problems, Yakutsk, Russia[1]
School of Higher Sportsmanship, Yakutsk, Russia[2]

The concentration of the serum tumor markers in people living in 6 different regions of the Republic of Sakha (Yakutia) was determined by an enzyme immunoassay, and the chemical composition of water used for drinking was evaluated. A total of 675 residents aged 18 to 79 years were examined. Increased concentrations of chemical substances (phosphates, fluorides, manganese, strontium, and lead) in water resulted in increased levels of tumor markers, such as AFP, CEA, PSA and CA-125.

Relevance

In Yakutia, with a rapid industrial growth, there has been an increase in the cancer incidence. Sewage water pollution cancer increases cancer risk [1, 2].

Material and Methods

A total of 675 residents aged 18 to 79 years living in 6 different regions of the Republic of Sakha (Yakutia), 461 men (mean age 45.01 ± 0.93) and 214 women (mean age 45.54 ± 0.56) were examined. The national composition of the surveyed persons was represented by 246 Yakuts, 194 by indigenous small-numbered peoples of the North (Evenki, Evens and Dolgans), 236 by a Russians, Tatars, etc.

Data on the chemical composition of water taken from water basins for drinking (the Matta River – the Magarass village, Gorny district; near intake the Lena River – the Modut village, Namsky district, «Pool Yasachnaya» – the Neplemennoe village of the Verkhnekolymsky District, the Peleduy River - the Vitim village of the Lensky District, the Aldan River - the Tommot Aldansky District) were provided by the Administration of the Hydrometeorological Service of the Republic of Sakha (Yakutia).

Blood for laboratory tests was taken from the ulnar vein in the morning on an empty stomach. The concentrations of tumor markers: alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), male prostate-specific antigen (PSA) in males, tumor-associated surface antigen (CA-125) in females, were determined by ELISA using Vector Best test kits (Novosibirsk, Russia).

Data of the chemical composition of water were provided by the Administration of the Hydrometeorological Service of the RS (Y).

Results

Of the 15 chemical substances, only 5 elements (phosphates, strontium, fluorides, manganese, calcium) showed reliable correlation with the concentration of tumor markers in the blood of the residents.