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Abiraterone and Docetaxel Treatments Increase Phospho-PTEN Expression in Metastatic Prostate Cancer Cells

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ABSTRACT

Aim: Prostate cancer is the second leading cause of death in cancer-related deaths in men. Docetaxel and abiraterone acetate are widely used in the treatment of castration-resistant metastatic prostate cancer. Phospho-PTEN triggers proliferation, migration, angiogenesis and survival in cells by causing oncogenic Akt hyperactivation. This study, it is aimed to investigate the effects of docetaxel and abiraterone acetate agents, which are widely used in the treatment of prostate cancer, on the expression of phospho-PTEN, which stimulates the oncogenic pathway.

Material and Methods: The effects of docetaxel and abiraterone acetate on phospho-PTEN expression in androgen receptor (+) and androgen receptor (-) metastatic prostate cancer cell lines were investigated in vitro by immunofluorescence method.

Results: Findings were compatible in both androgen receptor (+) and androgen receptor (-) metastatic prostate cancer cell lines. No statistically significant difference in phospho-PTEN expression was observed between the control and abiraterone acetate groups. Phospho-PTEN expression was increased statistically significant in docetaxel and abiraterone acetate+docetaxel groups compared to control. This increase was greater statistically significant in the combined group given the two agents compared to the docetaxel group.

Conclusion: A significant increase in phospho-PTEN was observed in the docetaxel and combined treatment groups. The increase of Phospho-PTEN causes oncogenic Akt hyperactivation. According to this information, docetaxel and combined drug treatments may support the oncogenic pathway in cells by increasing phospho-PTEN in patients. To eliminate these effects in patients, the administration of agents that dephosphorylate PTEN or agents that will stimulate the pathways that provide dephosphorylation may increase the total survival of the patients.

Keywords: Prostate; cancer; phospho-PTEN; docetaxel; abiraterone.

Abirateron ve Docetaxel Tedavileri Metastatik Prostat Kanseri Hücrelerinde Phospho-PTEN Ekspresyonunu Arttırır

ÖZ

Amaç: Prostat kanseri erkeklerde kanser ile ilişkili ölümlerde ikinci sırada yer almaktadır. Kastrasyona dirençli metastatik prostat kanseri tedavilerinde docetaxel ve abirateron asetat yaygın olarak kullanılmaktadır. Phospho-PTEN, onkojenik Akt hiperaktivasyonuna sebep olarak hücrelerde proliferasyon, migrasyon, angiyogenez ve hayatta kalmayı tetikler. Bu çalışmada prostat kanseri tedavisinde yaygın olarak kullanılan dosetaksel ve abirateron asetat ajanlarının onkogenic yolağı uyaran phospho-PTEN ekspresyonu üzerine etkisinin araştırılması amaçlanmışır.

Gereç ve Yöntemler: In vitro olarak antijen reseptör (+) ve androjen reseptör (-) metastatik prostat kanseri hücre hatlarında dosetaksel ve abirateron acetat'ın phospho-PTEN expresyonu üzerine etkisi immünofloresan yöntemi ile araştırılmıştır.

Bulgular: Antijen reseptör (+) ve androjen reseptör (-) metastatik prostat kanseri hücre hatlarının her ikisinde de bulgular birbiriyle uyumluydu. Kontrol ve abirateron asetat grupları arasında phospho-PTEN ekspresyonununda istatistiksel olarak anlamlı bir fark gözlenmedi. Docetaxel ve abirateron asetat+dosetaksel gruplarında phospho-PTEN ekspresyonu kontrole göre istatistiksel olarak anlamlı şekilde arttı. Bu artış iki ajanın birlikte verildiği kombine grupta

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dosetaksel grubuna kıyasla istatistiksel olarak anlamlı şekilde daha fazlaydı.
Sonuç: Dosetaksel ve kombine tedavi gruplarında belirgin şekilde phospho-PTEN artışı gözlendi. Phospho-PTEN'in artışı onkojenik Akt hiperaktivasyonuna neden olmaktadır. Bu bilgilere göre, dosetaksel ve kombine ilaç tedavileri hastalarda phospho-PTEN artışına sebep olarak hücrelerde onkojenik yolağı destekliyor olabilir. Hastalarda bu etkilerinin bertaraf edilebilmesi için PTEN'i defosforile edici ajanlar ya da defosforilasyonu sağlayan yolakların uyarılmasını sağlayacak ajanların verilmesi hastaların toplam hayatta kalma sürelerini artırabilir.
Anahtar Kelimeler: Prostat; kanser; phospho-PTEN; dosetaksel; abirateron.

INTRODUCTION

Prostate cancer (PCa) is the second most common type of cancer observed among men worldwide(1). Recent advances in prostate cancer screening and diagnosis enable the disease to be diagnosed at an early stage to a large extent. Early stage treatment options are more successful. Treatment at this stage may include surgery and radiation and is therapeutic. However, these treatments are only palliative in advanced and metastatic prostate cancer patients (2-4). In these patients, the initial response to androgen suppressive (castration) therapy, introduced by Huggins and Hodges in 1941, is quite good (5). Significant clinical regressions have been observed in patients receiving this therapy. However, approximately 12-18 months after the start of treatment, prostate cancer was observed to progress despite treatment (6). The result was that castration-insensitive prostate cancer emerged (Castration Resistant Prostate Cancer (CRPC). After the onset of progression, survival in these patients is around 18 months (2, 3, 7). Docetaxel is the first chemotherapy agent to increase survival in CRPC patients (8, 9). It has been shown that this chemotherapy agent binds beta tubulin in cell division causing microtubule stabilization and G2/M arrest, inhibition of nuclear translocation of androgen receptor, and apoptosis in cancer cells by B-cell lymphoma 2 (Bcl-2) phosphorylation (10). Despite this treatment, the progression of the disease may continue. Abiraterone acetate, a new agent approved for the treatment of prostate cancer about ten years ago, has been observed to increase the survival rate of patients in pre- and post-docetaxel treatments (11, 12). Abiraterone acetate is a selective inhibitor of cytochrome P450 c17, an important enzyme in testosterone synthesis. This agent blocks androgen biosynthesis in adrenal glands, testicles, and prostate tumor tissue (13-15).

Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) is one of the most important tumor suppressor genes. PTEN is a lipid phosphatase that dephosphorylates the 3 positions of phosphatidylinositol-(3,4,5)-triphosphate (PI(3,4,5)P3) on the inositol ring to form PI(4,5)P2 (16, 17). PTEN limits Akt activation at the cell membrane by inhibiting the activity of the oncogenic PI3K pathway. Akt activation promotes oncogenic processes such as survival, proliferation, angiogenesis and growth (18). Loss of the tumor suppressor PTEN is common in prostate cancer patients. Loss of PTEN is detected in approximately 25-30% of primary prostate cancer patients and approximately 40-60% of metastatic CRPC patients (19). In addition to the loss of PTEN, the phosphorylation of several critical phosphorylation sites in the PTEN C2 domain, including Ser-380, Thr382, and Thr383, causes PTEN inhibition. It has been shown that these phosphorylation sites increase the stability of PTEN and decrease the phosphatase activity of PTEN (20, 21). Phosphorylation of PTEN at S380 results in rapid migration of nuclear PTEN into the cytoplasm (22). It has also been shown that S380 phosphorylation of PTEN causes loss of phosphatase activity while stabilizing the protein against degradation (21, 23). In gastric carcinogenesis, the phosphorylation of PTEN from the ser380 region increased the tumorigenesis by causing inactivation of PTEN (24). In acute myeloid leucaemia (AML) and human fibro myomatous uteri, high levels of phosphorylation were detected in the Ser380/Thr382/Thr383 regions of PTEN (25, 26). Moreover, inactivation of the N-myc downstream-regulated gene 2 (NDRG2) gene, which is associated with a protein that ensures PTEN dephosphorylation, contributes to Akt hyperactivation by causing phosphorylation in the Ser380/Thr382/Thr383 regions of PTEN. In addition, it has been shown that the expression of this gene is decreased in many cancer types (27). It has been shown that increased expression of phospho-PTEN (Ser380) in prostate cancer cells causes Akt hyperactivation (28).

The loss of PTEN and the increase of phospho-PTEN expression are important for tumorigenesis and Akt hyperactivation, considering the studies conducted. In previous studies reviewed, there was not found any information on how abiraterone acetate and docetaxel affect phospho-PTEN expression. In this study, we aimed to investigate how abiraterone acetate and docetaxel, which are frequently used in the treatment of metastatic prostate cancer, affect the expression of phospho-PTEN, which causes PTEN inhibition and related Akt hyperactivation.

MATERIAL AND METHODS

Cell lines and Reagents

Androgen-sensitive LNCaP derived from subclavicular lymph node metastasis of prostate cancer and androgen-insensitive PC3 prostate cancer cell lines derived from bone metastasis were used in the study (ATCC, Manassas, VA, USA). Cells were cultured in RPMI 1640 medium containing 10% FBS (fetal bovine serum) and penicillin-streptomycin (100 U/mL-100 µg/mL) in a 37 °C incubator in a 5% CO2 environment. In the study, IC50 doses and incubation time (72 hours) were used, which have been determined for abiraterone acetate (AA) and docetaxel (DTX) (MedKoo Biosciences, Inc. Morrisville, USA) from our previous studies (29). The study consisted of the control group administered only DMSO, the AA group administered only abiraterone acetate, the DTX group administered only docetaxel and the AA+DTX groups in which both agents were administered together.

Immunofluorescence

Cells were seeded into chamber slides with approximately $2x10^4$ cells per well. After being incubated for 24 hours at 37 °C with 5% CO_2, AA and DTX were

incubated in the wells in the above-mentioned groups at the previously determined IC50 doses and for 72 hours. Chamber slides were washed with ice-cold PBS (phosphate buffer saline) and fixed with 1:1 methanol/acetone. The cells were permeabilized with 0.1% Triton-X-100 prepared with PBS and the cells were washed again. Primary antibody rabbit phospho-PTEN (Ser380, Cell Signaling #9551, 1:200 dilution) and secondary antibody goat anti-rabbit IgG (Alexa-fluor-488 labeled, 1: 500 dilution, Thermo Fisher Scientific, A-110034) were used. After imaging the immunostaining with a Zeiss AxioPlan fluorescence microscope (Carl Zeiss, Oberkochen, Germany), the staining intensities were analyzed with ImageJ software (http://imagej.nih.gov/ij/).

Statistical Analysis

All experiments were repeated at least three times. The expression level of at least 10 cells in each group was assessed by measuring with ImageJ. All data were analyzed with GraphPad Prism 9 (GraphPad Software) for statistical significance. Data were expressed as median (minimum-maximum) or mean ± standard deviation (SD), as appropriate. Data normality was assessed by the Shapiro–Wilk test. One-way ANOVA with Post Hoc Tukey test were used to evaluate the differences for multiple comparisons. $p<0.001$ were considered statistically significant.

RESULTS

LNCaP cell's immunofluorescence localization of phospho-PTEN was both cytoplasmic and nuclear. Phospho-PTEN expression was weak in the control and AA groups, and there was no statistically significant difference in expression between control and AA groups (Figure 1.A and 1.B) (p =0.887). Phospho-PTEN expression was strongly positive in DTX and AA+DTX groups. Phospho-PTEN expression was increased in DTX and AA+DTX groups compared to the control and AA groups, and this increase was statistically significant (Figure 1.A and 1.B) (p <0.001). In the AA+DTX group, phospho-PTEN expression was strongly positive (Figure 1.A). The phospho-PTEN expression of AA+DTX group showed a statistically significant increase compared to the DTX group (Figure 1.A and 1.B) (p <0.001).

The expression of phospho-PTEN in PC3 cells was both cytoplasmic and nuclear and was also consistent with LNCaP cells. Phospho-PTEN expression was weakly positive in the control and AA groups, and the expression level of both groups was similar (Figure 2.A and 2.B) (p =0.333). DTX and AA+DTX groups phospho-PTEN expression was strongly positive (Figure 2.A). The nuclear structures of the cells of these groups were different and atypical from the control and AA groups (Figure 2.A). DTX and AA+DTX groups had higher phospho-PTEN expression than control and AA groups, and this difference was statistically significant (Figure 2.A and 2.B) (p <0.001). In the AA+DTX group, phospho-PTEN expression was increased statistically significant more than the DTX group (Figure 2.A and 2.B) (p <0.001).

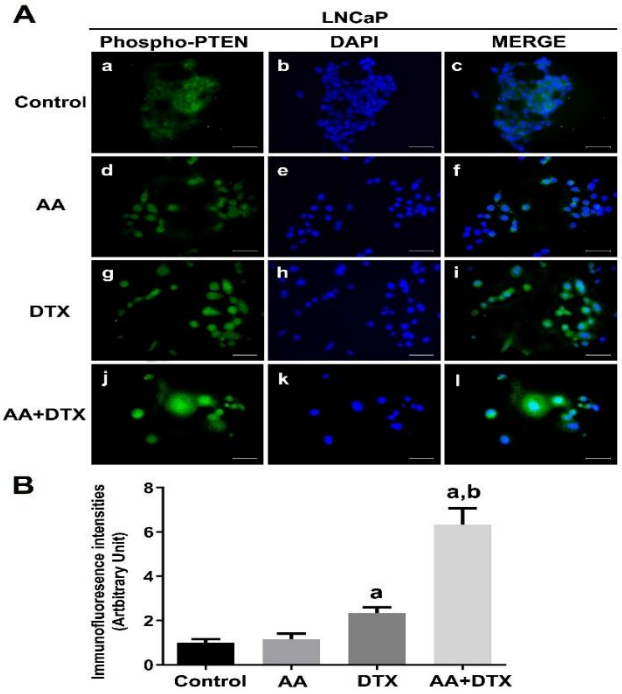

Figure 1.A. Phospho-PTEN immunofluorescent staining images in the androgen-sensitive LNCaP prostate cancer cell line. **B.** Statistical plot of immunofluorescence results after ImageJ analysis. Error bars are shown as mean ± SD. Statistical significance ($p<0,001$) compared with [a]control and AA, [b]DTX. AA; Abirateron asetat, DTX; Docetaxel. Scale bar is 40 µm.

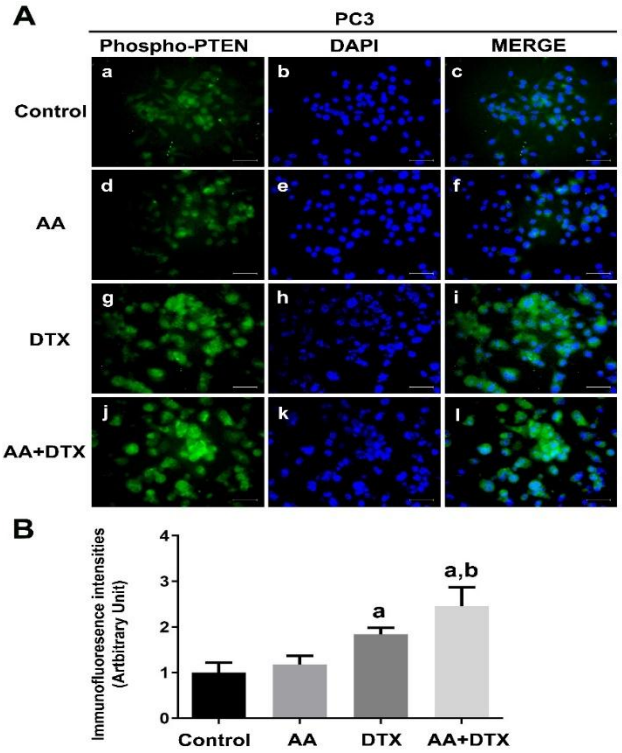

Figure 2. A. Phospho-PTEN immunofluorescent staining images in the androgen-insensitive PC3 prostate cancer cell line. **B.** Statistical plot of immunofluorescence results after ImageJ analysis. Error bars are shown as mean ± SD. Statistical significance ($p<0,001$) compared with [a]control and AA, [b]DTX. AA; Abirateron asetat, DTX; Docetaxel. Scale bar is 40 µm.

DISCUSSION

In the United States, it is predicted that approximately 268,500 people will be diagnosed with prostate cancer and 34,500 will die this year (30). Prostate cancer is the second most common cancer among men worldwide (1). Abiraterone acetate and docetaxel are commonly used in the treatment of late stage and metastatic prostate cancer patients (31). Despite these treatments, prostate cancer mortality rates are still high. Therefore, it is important to elucidate the molecular mechanisms that these treatments affect in cells to increase their effectiveness. PTEN controls the activation of the Akt pathway, which supports oncogenic processes such as survival, angiogenesis, migration and proliferation (18). Loss of PTEN has been observed in many cancers (19). In addition, phosphorylation of PTEN causes hyperactivation of Akt in many cancers (27). In our study, we investigated the effects of abiraterone acetate and docetaxel, which are widely used in prostate cancer treatments, on the expression of phospho-PTEN, which causes oncogenic Akt hyperactivation, in LNCaP and PC3 metastatic prostate cancer cell lines.

Abiraterone acetate and docetaxel treatments caused changes in Phospho-PTEN expression in LNCaP and PC3 cells. DTX and AA+DTX treatment groups increased Phospho-PTEN expression in LNCaP and PC3 cell lines compared to control and AA groups. It is known that tumor suppressor PTEN is lost in patients with organ-confined and metastatic prostate cancer (19). Modifications and mutations on the PTEN protein cause inhibition of this protein and a decrease in its tumor suppressor properties. In particular, it causes inhibition of phosphorylation from Ser-380, Thr382 and Thr383 regions located on the C2 domain of PTEN (20,21). PTEN loss and phosphorylation cause oncogenic Akt hyperactivation. Akt hyperactivation causes proliferation, metastasis, survival and angiogenesis (18). Phosphorylation causing this PTEN inhibition is also present in prostate cancer cells, and this phosphorylation caused Akt hyperactivation (28). Phospho-PTEN expression is also increased in acute myeloid leucaemia (AML), human fibromyomatous uteri and gastric carcinogenesis (24-26). Moreover, it has been determined that NDRG2 expression, a gene that provides PTEN dephosphorylation, that is, inhibits oncogenesis, is decreased in liver, stomach, glioblastoma and colon cancers (27). In LNCaP (AR+) and PC3 (AR-) cell lines, phospho-PTEN expression was increased in the combined treatments of docetaxel and abiraterone acetate. Considering the previous studies, when we evaluate our results; while docetaxel supports tumor suppression by stabilizing microtubule and G2/M arrest in prostate cancer cells, (10) according to our findings, it has been observed that it supports the oncogenic pathway by increasing phospho-PTEN expression in cancer cells. Combined treatment of docetaxel and abiraterone acetate caused overexpression of phospho-PTEN, which causes oncogenic Akt hyperactivation, although it appears to be a potent tumor suppressor with both microtubule stabilization and inhibition of androgen synthesis in prostate cancer cells. Treatments of docetaxel alone and in combination with abiraterone acetate provide an increase in patient survival with tumor suppressor mechanisms in the early stages of treatment in prostate cancer cells. Increasing phospho-PTEN expression may decrease the recurrence-free survival and total survival of the patients. In our previous study, we have determined that docetaxel and abiraterone acetate increased HES1 expression in prostate cancer cells (29). Increased HES1 expression in prostate cancer suppresses PTEN expression (32). Therefore, docetaxel and abiraterone acetate act as tumor suppressors by suppressing PTEN expression via HES1, while the use of docetaxel and abiraterone acetate+docetaxel play an oncogenic role by increasing phospho-PTEN expression.

CONCLUSION

The use of docetaxel alone or in combination with abiraterone acetate may cause poor prognosis by increasing phospho-PTEN expression and proliferation, angiogenesis, migration and survival of cancer cells, especially in metastatic prostate cancer patients. The use of an agent that will provide PTEN dephosphorylation or cause the activation of genes that provide dephosphorylation with these agents may improve the prognosis of the patients. Many new studies are needed to develop these applications and agents and make them usable in patients.

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