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The expression of Platelet-Derived Growth Factor Receptors (PDGFRs) and their correlation with overall survival of patients with ovarian cancer

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ABSTRACT

Objectives: The main aim of the study was to investigate the expression of Platelet-Derived Growth Factor Receptors alpha (PDGFR-alpha) and beta (PDGFR-beta) in malignant and benign ovarian tumors. We performed an analysis of the correlation of PDGFRs expression and stage of the disease, tumor grade and histopathological type of epithelial ovarian cancer (EOC). Additionally, we evaluated patient prognosis according to PDGFR expression.

Material and methods: Our study group was composed of 52 samples of EOCs, 35 samples of benign ovarian tumors (BOTs), and 21 samples of unchanged ovaries (UOs). The samples were collected from patients who had been operated on in the Division of Gynecological Surgery of the Poznan University of Medical Sciences.

Results: PDGFR-alpha was found to be expressed more frequently in cancer cells of EOCs, when compared with tumor cells of BOTs and epithelium of UOs. On the other hand, PDGFR-alpha receptors were present less frequently in the stroma of EOCs, when compared with the stroma of BOTs and UOs. Comparing the studied groups, there were no statistically significant differences in the expression of PDGFR-beta. The expression of both PDGFRs was not related to the FIGO stage, grade or histopathological type of EOCs. The expression of the PDGFR-beta receptor in cancer cells was associated with an improved overall survival among patients with EOCs. Patient prognosis was not affected by either PDGFR-alpha expression or by PDGFR-beta tumor stroma expression.

Conclusions: The expression of PDGFR-alpha is significantly different when comparing EOCs, BOTs and UOs. However, the prognosis of EOC only seems to be affected by PDGFR-beta expression in cancer cells.

Key words: platelet-derived growth factor; platelet-derived growth factor receptor; ovarian malignancies, epithelial ovarian cancer

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INTRODUCTION

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecological malignancies and the fifth leading cause of cancer-related death among women in the Western World [1]. Although complete remission after primary treatment is achieved in approximately half of patients, the majority will relapse, and the disease then becomes fatal [2, 3]. The poor prognosis of ovarian cancer patients has motivated the development of new anti-cancer therapies. Recently, antiangiogenic treatments have been introduced, and several trials have reported encouraging results in the management of patients with ovarian cancer. Two 3rd phase clinical trials evaluated the addition of anti-VEGF monoclonal antibody (bevacizumab) to the primary chemotherapy in patients with ovarian cancer [4]. However the results were far from what was expected — only the ICON7 study indicated a pro-

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longed overall survival rate in the group of patients with high-risk, non-optimally debulked ovarian cancer [5].There are multiple theories trying to explain lack of the efficacy of an anti-VEGF blockade, and one of them postulates the role of other than VEGF proangiogenic factors, which may stimulate the development of new blood vessels [6]. Thus, it is believed, that a combined inhibition of various proangiogenic pathways may exert more pronounced clinical benefits [7].

One group of growth factors which contributes to angiogenesis are the platelet-derived growth factors (PDGFs). The PDGFs family includes five growth factors: PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD. These growth factors are homo- or hetero-dimers, each composed of two of the following polypeptides: PDGF-A, PDGF-B, PDGF-C, and PDGF-D. The PDGFs are ligands for receptors: PDGFR-alpha (for PDGF- AA, AB, BB, CC) and PDGFR-beta (for PDGF-BB, DD and less for AB). PDGFs play an important role in many physiological and pathological processes — like wound healing, bone development, erythropoiesis, atherosclerosis, and fibrosis. They act as typical growth factors, thus, they also play a role in cancerogenesis [8]. PDGF-PDGFR pathway activation is observed in multiple steps essential for cancer development, including uncontrolled proliferation, evading growth suppressors, resisting cell death, infiltration, metastasis, and immune system evasion [9–12]. Matei et al. [13], have shown that autocrine activation of PDGFR-alpha stimulates proliferation of ovarian cancer cells. Lassus et al. [14] reported that the expression of PDGFR-alpha in serous ovarian cancer cells correlates with a high mitotic index. Furthermore, inhibition of PDGFR signaling leads to tumor cell apoptosis, and a decrease in microvascular density and of the tumor cell proliferation rate [15]. Matsuo et al. [16], showed that blocking PDGFR-alpha activity with monoclonal antibodies increases the sensitivity of carcinoma cells to docetaxel. PDGFs are also suspected to facilitate angiogenesis during cancer development. PDGF-AA, PDGF-BB, and PDGF-AB are expressed within endothelial cells (ECs). Of these three growth factors, probably PDGF-BB has the most important impact on angiogenesis, as it directly stimulates ECs proliferation, migration, and tube formation, and inhibits ECs apoptosis [17]. Additionally, PDGF-B action through PDGFR-beta is responsible for pericyte vessel coverage, and thus, for vessel maturation [18, 19]. On the other hand, it was shown that significant vascular abnormalities develop in PDGFR-alpha knockout mice [20]. PDGFs can also indirectly stimulate angiogenesis by increasing expression of VEGF [21]. Furthermore, recent studies indicate PDGFs are involved not only in vascular development, but they also have a prominent role in lymphaniogenesis [22]. Taken together, these data support the important role of PDGFs in ovarian cancer development and angiogenesis.

Recently, protein kinase inhibitors, targeting among others the PDGF-PDGFRs axis, were introduced for clinical trial in ovarian cancer [4]. However, targeted therapy requires the appropriate selection of patients who may benefit from this novel therapy. Thus, the main aim of our study was to investigate the expression of PDGFR-alpha and PDGFR-beta in epithelial ovarian cancer. We have compared the expression of both receptors with their presence in BOTs and UOs. Additionally, we performed an analysis of PDGFRs expression and its correlation with selected clinicopathological features of the disease. Finally, because data on the impact of PDGFRs expression on EOC patient prognosis is sparse, we evaluated the expression of PDGFRs in terms of the overall survival (OS) rates of patients with EOC.

MATERIAL AND METHODS

The study group was composed of 52 samples of epithelial ovarian cancer (EOCs). All samples were collected from patients operated on in the Division of Gynecological Surgery, at the Poznan University of Medical Sciences, during primary surgery. The control group included 35 benign ovarian tumors (BOTs) and 21 samples of unchanged ovaries (UOs) obtained for non-oncological reasons. The tumors and ovarian samples were fixed in 10% formalin for immunohistochemical study. The expression of PDGFR-alpha and PDGFR-beta was assessed by means of immunohistochemistry using the ImmunoMax technique [23]. The following antibodies were used for the immunohistochemical evaluation: PDGF Receptor alpha – monoclonal mouse anti-human antibody; dilution 1:1000; clone MM0004-8A89, Novus Biologicals®, catalogue number: NB110-60969; and PDGF Receptor beta – monoclonal mouse anti-human antibody; dilution 1:500, clone MM0005-5C37, Novus Biologicals®, catalogue number: NB110-60970. Both, the tumor cells/ovarian epithelium and tumor/ovarian stroma were evaluated for the presence of the PDGFR-alpha and -beta. We observed only cytoplasmic PDGFRs staining pat tern, both in the tumors and in the UOs. The expression of PDGFRs was evaluated using subjective assessment of PDGFRs immunoreactivity. The PDGFRs expression was assessed as negative, when less than 5% of cells presented immunoreactivity for PDGFR. Representative images are presented in the Figure 1.

Forty patients were available for follow-up. In this group, the patients' survival rates were analyzed in relation to PDGFRs expression. The median patient follow-up was 1238 days (range 28–4550). Information on patients who died was retrieved from the database of the regional office of the National Health System of Poland.

The statistical analysis was performed using MedCalc (11.4.2.0) and GraphPad (3.06) software. The distribution of the variables in the study groups was verified using the Shapiro-Wilk test. Parametric or non-parametric tests were

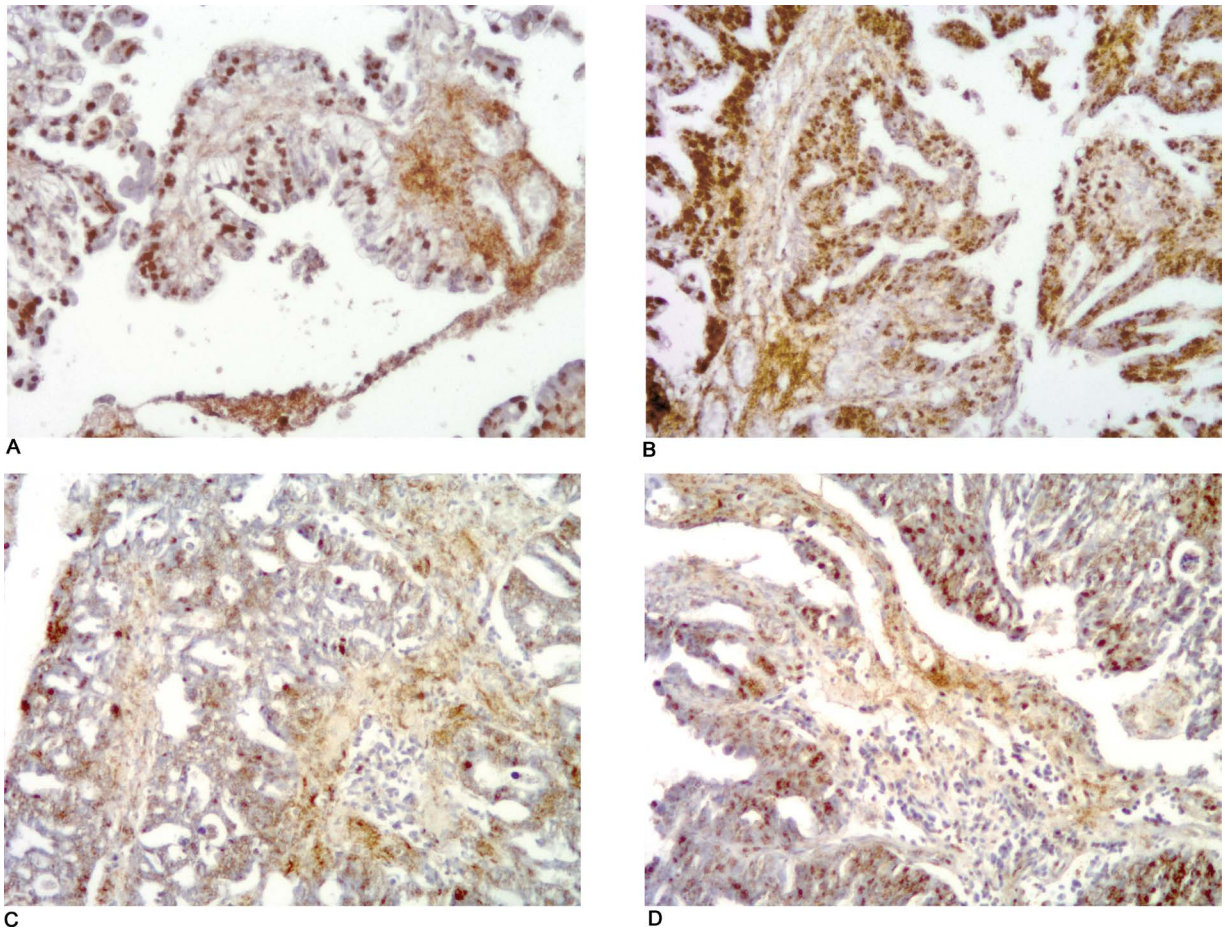

Figure 1. Representative pictures of PDGFRs expression in cancer cells and tumor stroma. **A.** Ovarian serous adenocarcinoma with strong PDGFR-alpha immunoreactivity in cancer cell cytoplasms, and moderate PDGFR-alpha immunoreactivity in the tumor stroma. **B.** The same tumor as on the picture A, showing strong PDGFR-beta immunoreactivity in cancer cell cytoplasm, and moderate PDGFR-beta immunoreactivity in the tumor stroma. **C.** Ovarian serous adenocarcinoma with weak PDGFR-alpha immunoreactivity in cancer cell cytoplasms, and weak PDGFR-alpha immunoreactivity in the tumor stroma. **D.** The same tumor as on the picture C, showing moderate PDGFR-beta immunoreactivity in cancer cell cytoplasm, and weak PDGFR-beta immunoreactivity in the tumor stroma. Magnification 200x for A–D

used for evaluation according to the data distribution. The differences in patient age and BMI were determined using the Kruskal-Wallis Test with post-hoc Dunn's Multiple Comparisons Test. The differences between the expressions of PDGFRs between studied groups were analyzed using the Fisher exact test. In the case of malignant ovarian tumors, the Fisher exact test was also used for the analysis of the differences in PDGFRs expression according to the tumor grade and the FIGO stage of the disease. We have used Chi square test for the analysis of PDGFR expression according to the histopathological type of the disease. Survival analysis was conducted using Kaplan-Meier survival curves and the differences in patient survival were determined using log-rank test.

Our research plan was approved by the University of Medical Science Poznan's Bioethical Committee (Number: 181/07).

RESULTS

The median age of patients in the group with EOCs was 53 years (range: 34–85), whereas in the group with BOTs it was 43 years (14–80). The median age in the UOs group was 50 years (44–67). The difference between the patients' ages was statistically significant ($P = 0.002$), whereas the posthoc tests only showed statistically significant differences between the group with malignant ovarian tumors and that with benign ovarian tumors ($P < 0.01$). The median body mass index (BMI) in the group with EOCs was 25.7 (range: 17.9–49.7), while in the group with BOTs and in the UOs group, the median BMI was 24.8 (18.5–37.3) and 25.2 (17.8–29.4) respectively. This latter difference was not statistically significant ($P = 0.199$).

The histopathological diagnoses of the tumors are summarized in Table 1. Among the EOCs there were nine tumors at stage I, 10 at stage II, 24 at stage III and 9 at (FIGO) stage IV.

Table 1. Histopathological diagnoses of ovarian tumors in the study group	
Malignant ovarian tumors group (n = 52)	
Serous adenocarcinoma	25
Mucinous adenocarcinoma	8
Endometrioid adenocarcinoma	4
Clear — cell adenocarcinoma	4
Undifferentiated carcinoma	11
Benign ovarian tumors group (n = 35)	
Serous cystadenoma	10
Mucinous cystadenoma	5
Endometrioma	7
Adult teratoma	10
Fibrothecoma	3

Grading of malignant tumors was as follows: G1 — 11 tumors, G2 — 10 tumors and G3 — 31 tumors.

The expression of the PDGF-alpha receptor was analyzed in 52 samples of EOCs, in 34 BOTs and in 18 samples of UOs, while the expression of the PDGF-beta receptor was analyzed in 52, 35 and 18 samples respectively. PDGFR-alpha expression was found in neoplastic cells in 33% of the malignant ovarian tumors and in 20% of the benign ovarian tumors. There was no PDGFR-alpha expression in the epithelium of the UOs. PDGFR-alpha expression between each of the groups studied was found to differ, and the difference was statistically significant (P = 0.008). Similarly, there were statistically significant differences in PDGFR-alpha expression in the analyzed groups (P = 0.005). PDGFR-alpha was found in the stroma of 83% of the UOs, 40% of the EOCs and in 58% of the BOTs. There were no significant differences in the expression of PDGFR-beta between the studied groups, both in either of the neoplastic cells/epithelium (P = 0.07) or the stroma (P = 0.29). The PDGF receptors expression results are shown in Table 2.

PDGFR-alpha expression differed in neither the tumor cells (P = 0.76) nor in the stroma (P = 0.55) between early and advanced malignant ovarian tumors (Tab. 3). Similarly, PDGFR-beta expression did not differ between the analyzed subgroups (tumor cells — P = 0.09; stroma — P = 0.76). There were no differences in PDGFRs expression between the EOCs of G1 and G2/3. These results are shown in Table 4.There were no differences in the expression of PDGF receptors between different histological types of ovarian cancer. Those results are summarized in Table 5.

Patients with PDGFR-beta expression in cancer cells of EOC (10 patients) had significantly higher median OS compared with patients without PDGFR-beta expression (30 patients) in cancer cells (3506 days, range 526–3966 vs 891 days, 28–4550, respectively, P = 0.04). There was no significant difference regarding patient survival in relation to PDGFR-beta expression in the stroma of EOC. Patients with PDGFR-beta expression in the tumor stroma (21 patients) had a median survival of 1247 days (range

Table 2. Expression of alpha and beta receptors for PDGF in epithelial ovarian cancer, benign ovarian tumors,and unchanged ovaries

	Malignant ovarian tumors	Benign ovarian tumors	Unchanged ovaries	P value
PDGFR-alpha neoplastic cells/epithelial cells	33% (17/52)	20% (7/34)	0 (0/18)	P = 0.008
PDGFR-alpha stroma neoplasm/normal ovary	40% (21/52)	58% (20/34)	83% (15/18)	P = 0.005
PDGFR-beta neoplastic cells/epithelial cells	23% (12/52)	14% (5/35)	0 (0/18)	P = 0.07
PDGFR-beta stroma neoplasm/normal ovary	63% (33/52)	50% (17/35)	67% (12/18)	P = 0.29

Table 3. Expression of PDGF receptors according to FIGO stage

	FIGO I and II	FIGO III and IV	P value
PDGFR-alpha carcinoma cells (+)	37% (7/19)	30% (10/33)	P = 0.76
PDGFR-alpha stroma (+)	47% (9/19)	36% (12/33)	P = 0.55
PDGFR-beta carcinoma cells (+)	37% (7/19)	15% (5/33)	P = 0.09
PDGFR-beta stroma (+)	68% (13/19)	60% (20/33)	P = 0.76

Table 4. Expression of PDGF receptors according to tumor grade

	G1	G2/3	P value
PDGFR-alpha carcinoma cells (+)	36% (4/11)	32% (13/41)	P = 1.0
PDGFR-alpha stroma (+)	54% (6/11)	37% (15/41)	P = 0.31
PDGFR-beta carcinoma cells (+)	27% (3/11)	22% (9/41)	P = 0.68
PDGFR-beta stroma (+)	64% (7/11)	63% (26/41)	P = 1.0

Table 5. Expression of PDGF receptors between different histopathological types of ovarian cancer

	Serous adenocarcinoma	Mucinous adenocarcinoma	Endometrioid adenocarcinoma	Clear — cell adenocarcinoma	Undifferentiated carcinoma	P value
PDGFR-alpha carcinoma cells (+)	36% (9/25)	37.5% (3/8)	0% (0/4)	25% (1/4)	35.7% (4/11)	P = 0.67
PDGFR-alpha stroma (+)	40% (10/25)	50% (4/8)	25% (1/4)	0% (0/4)	54.5% (6/11)	P = 0.36
PDGFR-beta carcinoma cells (+)	24% (6/25)	37.5% (3/8)	25% (1/4)	0% (0/4)	21.4% (2/11)	P = 0.68
PDGFR-beta stroma (+)	64% (16/25)	75% (6/8)	25% (1/4)	50% (2/4)	54.5% (6/11)	P = 0.52

28–4550), when compared with 1229 days (range 106–3402) for the patients without PDGFR-beta expression in the tumor stroma (P = 0.84). Patient prognosis was unaffected by PDGFR-alpha expression. Patients with PDGFR-alpha expression (10 patients) in cancer cells had a median survival of 2314 days (range 526–4550), while patients with no PDGFR-alpha expression (30 patients) in cancer cells had a median OS of 1012 (28–3966 days; P = 0.19). Patients with PDGFR-alpha expression in tumor stroma (14 patients) had an insignificantly higher median OS compared with patients without PDGFR-alpha expression (26 patients) in tumor stroma (1924 days, range 364–4550 vs 913 days, 28–3966, respectively, P = 0.40). Figure 2 presents the survival curves corresponding to the elements referred to here.

DISCUSSION

In our study we observed significant differences in PDGFR-alpha expression between EOCs, BOTs and UOs. The differences were found both in the cancer cells and in the tumor stroma. On the other hand, there were no differences in the expression of PDGFR-beta between the groups analyzed. Henriksen et al. assessed the expression of alpha and beta receptors for PDGF in ovarian cancer, benign ovarian tumors and normal ovaries [24]. They demonstrated PDGFR-alpha expression in 16 of the 45 malignant ovarian tumors, while they found no expression in the BOTs and the UOs. Expression in the stroma occurred in 17 of the 45 malignant tumors, 9 of the 20 benign tumors and in all of the normal ovaires. These results are very similar to ours, except for the expression of PDGFR-alpha in the benign tumors, which occurred in 20% of the tumors in our study. Additionally, we have found PDGF-alpha expression in the stroma of 83% of the UOs [24]. Madsen et al. [25] observed PDGFR-alpha expression in cancer cells in 43% of EOCs, and in 32% of their stroma. A study by Wilczynski et al. [26] revealed similar results, namely, PDGFR-alpha expression in 58% ovarian cancers and no expression in the epithelium of normal ovaries. We may conclude that the findings of these reports are compatible. In summary, about 30–58% of EOC express PDGFR-alpha in cancer cells. PDGFR-alpha expression is less frequently presented in benign ovarian tumors. Three reports showed no expression of PDGFR-alpha in normal ovarian surface epithelium. In the case of PDGFR-alpha expression in the stroma, PDGFR-alpha immunoreactivity in the stroma is found in about one-third of EOCs, one-half of BOTs, and in most UOs.

The main difference between our study and the study by Henriksen et al. is the expression of PDGFR-beta in neoplastic cells. Henriksen et al. did not observe PDGFR-beta expression in either ovarian cancer or benign ovarian tumors cells, nor in normal ovarian epithelial cells. However, our study showed PDGFR-beta expression in 20% of ovarian cancers and 14% of benign ovarian tumors. The presence of PDGFR-beta expression in ovarian cancer cells

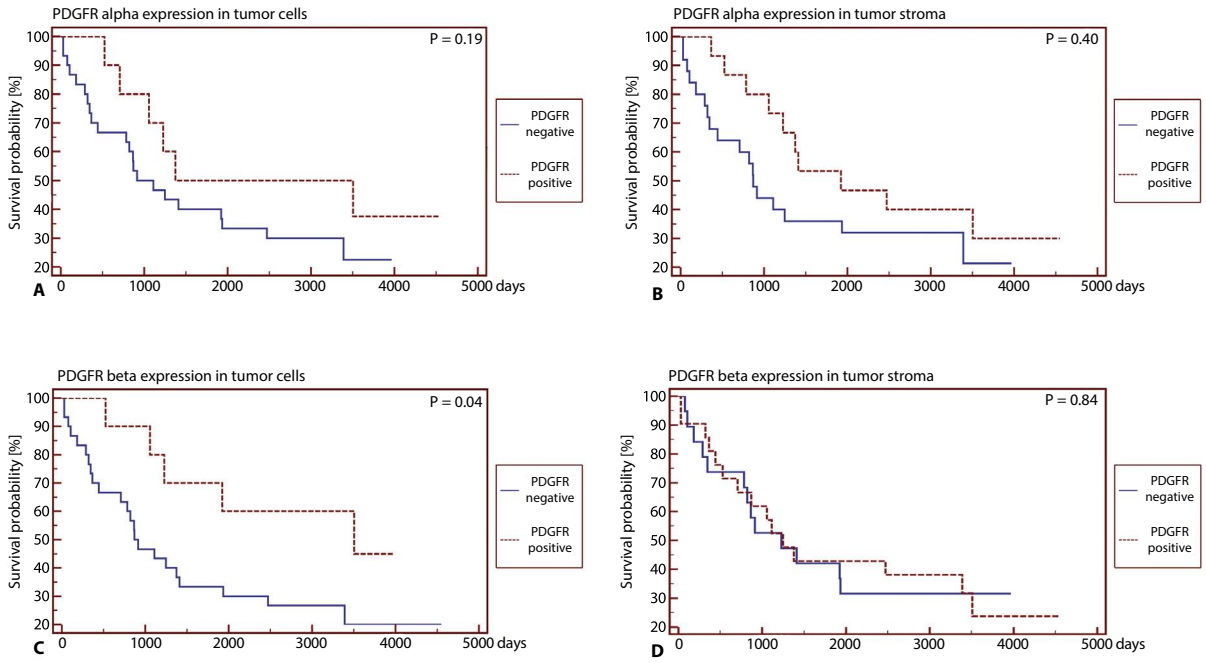

Figure 2. Survival analyses according to PDGFR expression. **A)** Patients with PDGFR-alpha expression (10 patients) in cancer cells of EOC had a median overall survival (OS) of 2314 days (range 526–4550), vs 1012 days (28–3966) for the patients with no PDGFR-alpha expression (30 patients) in cancer cells (P = 0.19). **B)** Patients with PDGFR-alpha expression in tumor stroma (14 patients) had a median n median OS of 1924 days (range 364–4550) vs 913 days (28–3966) for the patients without PDGFR-alpha expression (26 patients) in tumor stroma (P = 0.40). **C)** Patients with PDGFR-beta expression (10 patients) in cancer cells of EOC had a median OS of 3506 days (range 526–3966) vs 891 days (28–4550) for the patients without PDGFR-beta expression (30 patients) in cancer cells (P = 0.04). **D)** Patients with PDGFR-beta expression in the tumor stroma (21 patients) had a median survival of 1247 days (range 28–4550) vs 1229 days (range 106–3402) for the patients without PDGFR-beta expression in the tumor stroma (P = 0.84)

was also confirmed by other studies [24]. Apte et al. [15, 17] reported both PDGFR-alpha and PDGFR-beta expressions in ovarian cancer cells from HeyA8 and SKOV3ip1 cell lines. Madsen et al. and Wilczynski et al. [25, 26] reported PDGFR-beta expression in 41% and 29% of ovarian cancers respectively.

Madsen et al. [25] showed PDGFR-beta expression in the stroma of 44% of ovarian cancers. Henriksen et al. [24] reported PDGFR-beta expression in the stroma of 20 of the 21 unchanged ovaries studied, 21 of the 23 benign tumors, and 29 of the 45 ovarian cancers. The results of the two studies cited here corresponded with our observations.

Henriksen et al. showed more frequent expression of PDGFR-alpha in serous ovarian cancer than in mucinous and endometrioid. In our study there were no statistically significant differences in the expression of PDGFR-alpha between the various histopathological types of malignant ovarian tumors. Madsen et al. also did not find a correlation between PDGFRs expression and the histopathological type of the tumor. In the Henriksen et al. [24] study previously cited, the authors showed no differences in the expression of PDGF receptors between the different grades and stages of malignant tumors; and this finding also corresponds with our results. Similarly, no relationships were noted between PDGFRs expression and tumor stage and grade in the study by Madsen et al. [25].

In our study we found the expression of PDGFR-beta receptor in cancer cells to be associated with improved overall survival of EOCs patients. Similar results were obtained by Dabrow et al. [27], who reported a two times higher median relapse-free survival in patients with PDGFR-beta expression in cancer cells. These results are in contrast to those of the study by Avril et al. [28], which found high expression of PDGFR-beta to be associated with shortened survival rates and with platinum-resistance. However, both we and Dabrow et al. have based our study on immunohistochemistry techniques (assessment of PDGFR-beta immunoreactivity), while Avril et al. used reverse phase protein arrays to evaluate protein expression [27, 28]. Thus, the differences between the two sets of results may be explained by the studies' different methods of assessment.

We found no differences in EOC patient survival relating to the expression of PDGFR-beta in tumor stroma. Similarly, in the study by Madsen et al. [25], PDGFR-beta expression in tumor stroma did not affect patient survival. PDGFR-beta is expressed by a variety of non-cancerous cells infiltrating the tumor stroma, mainly Cancer-Associated Fibroblasts (CAFs) and pericytes. CAFs contribute to tumor stroma re-

modeling, creating a tumor-friendly microenvironment. Multiple studies confirm the role of tumor stroma and CAFs in ovarian cancer development and progression [29, 30]. Additionally, the number of CAFs seems to correlate with patients' poor prognosis, since EOC patients with stroma-rich tumors have a worse prognosis than patients with tumors characterized by poorly developed stroma [31]. On the other hand, recent studies have shown that pericyte coverage of vessels, by preventing cell migration and hematogenous metastasis, correlates with better patient prognoses [32]. In our paper we did not differentiate PDGFR-beta expressing stroma cells. We presume that further studies evaluating the source of PDGFR-beta expression in tumor stroma may contribute to a better understanding of the prognostic role of PDGFR-beta expression in the stroma of EOCs.

In our study, patient prognoses were not affected by PDGFR-alpha expression. Similar results were obtained by Madsen et al. [25]. However, in the study by Henriksen et al., patients with tumors expressing PDGFR-alpha in cancer cells had significantly shortened overall survival when compared with those with PDGFR-alpha negative tumors. The association was also significant, when the evaluation was limited to twenty-three stage III EOC patients [24]. Similar results were obtained by Matsuo et al. [16], where the authors found that increased PDGFR-alpha expression is associated with poorer overall survival when compared with low, or no, PDGFR-alpha expression. Our study did not confirm the above observations. The discrepancy between these three studies may be explained by the fact that each of the studies was based on small populations of patients. Additionally, there is significant variability in the specificity of various sets of anti-PDGFR-alpha antibodies. Thus, the different antibodies used in each of the studies may have influenced the differences between the studies' results [33].

Several trials have been conducted to evaluate the clinical utility of multipotential kinase inhibitors in the management of EOC. These drugs inhibit numerous signaling pathways involved in cancer development, including those of PDGFR-alpha and -beta. However, most of these drugs yield weak clinical responses, with no impact on patient prognosis [34]. The most promising results are related to the use of cediranib. Cediranib is a tyrosine kinase inhibitor that inhibits not only PDGFR-beta, but also all three members of the VEGFR family and c-KIT. A recent trial by Ledermann et al. [35] has shown significant prolongation of progression-free survival with cediranib when given during chemotherapy and then continued as maintenance therapy in women suffering from platinum-sensitive EOC. However, considering that PDGFRs are expressed in less than half of EOC patients, and their impact on patient prognosis is not clear, it seems reasonable to investigate PDGFR when conducting trials of PDGFR-inhibitors.

CONCLUSIONS

The expression of PDGFR-alpha, in contrast to PDGFR-beta, is significantly different between EOCs, BOTs and UOs. The expression of both PDGFRs is not affected by the clinical stage of the diseases, the tumor grade and the histopathological type of EOC. The prognostic role of PDGFR-alpha expression in EOC needs further evaluation. However, the prognosis of EOC seems to be affected by PDGFR-beta expression in cancer cells.

Conflict of interests

All authors have approved the final article and declare no conflicts of interest in relation to the current work.

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