International Journal of Gynecology and Obstetrics (2005) **88**, 292—298

International Journal of
GYNECOLOGY
& OBSTETRICS

www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

Serum tumor necrosis factor alpha receptors p55/p75 ratio and ovarian cancer detection

P. Rzymski[a,*], T. Opala[a], M. Wilczak[b], J. Woźniak[a], S. Sajdak[c]

[a]*Department of Mother's and Child's Health, Karol-Marcinkowski University of Medical Sciences, Polna St 33, 60-535 Poznan, Poland*
[b]*Department of Educational Medicine, Karol-Marcinkowski University of Medical Sciences, Polna St 33, 60-535 Poznan, Poland*
[c]*Department of Gynaecologic Surgery, Karol-Marcinkowski University of Medical Sciences, Polna St 33, 60-535 Poznan, Poland*

Received 9 September 2004; received in revised form 9 December 2004; accepted 22 December 2004

KEYWORDS
TNFα receptors;
p55;
p75;
CA-125;
Ovarian cancer;
Tumor markers

Abstract

Objective: Early ovarian cancer detection is still very difficult and patients are mostly in advanced stages, with obvious influence on poor prognosis. *Method:* Fifty-one ovarian cancer patients and 16 healthy controls had the serum concentrations of TNFα receptor p55, p75 and CA-125 measured prospectively and preoperatively. *Result:* Mean concentrations of TNFα receptor p55, p75 and CA-125 in patients with ovarian cancer were higher than in controls. The ratios of p55 and p75 receptor in ovarian cancer and controls were 0.73 ± 0.38 and 0.55 ± 0.06 respectively. The areas under ROC curve in detecting malignancy (all FIGO stages) were 0.73, 0.65, 0.88 and 0.85 for p55, p75, p55/p75 ratio and CA-125 respectively. The areas under ROC curve in detecting stage I of ovarian cancer were 0.52, 0.60, 0.84 and 0.66 for p55, p75, p55/p75 ratio and CA-125 respectively. *Conclusion:* Serum TNFα p55/p75 ratio showed promising value in ovarian cancer detection.

1. Introduction

In spite of rapid development of biophysical and biochemical diagnostic tools, the possibilities of early detection of ovarian cancer are still limited. Often this malignancy is detected late, with obvious influence on poor prognosis.

* Corresponding author. Tel.: +48 605 393096; fax: +48 61 8419288.
E-mail address: parzymsk@gpsk.am.poznan.pl (P. Rzymski).

0020-7292/$ - see front matter © 2005 International Federation of Gynecology and Obstetrics. Published by Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijgo.2004.12.015

The tumor necrosis factor alpha (TNFα) is a common mediator of apoptosis, inflammation and immune response. It is overproduced in cachectic patients with malignancies. But TNFα alone is capable of cytotoxic effect against cancer cells [1]. Its role in ovarian biology remains unclear. Some in vitro studies proved the stimulatory effect of this cytokine on normal ovarian cells with simultaneous inhibitory activity to cancer cells. Wu et al. [2] support the opposite opinion, that TNFα has also stimulatory effect on malignant cells.

The effect of TNFα is regulated by its two receptors, p55 (CD120a) and p75 (CD120b). The signal is transferred into the cell via a complicated protein system to target transcription proteins: nuclear factor κB (NF-κB) and c-*Jun*. This pathway results in activation of DNA regions responsible for cell growth, death, carcinogenesis and stress response [3]. Many studies showed the dominating role of receptor I (p55) in signal transduction, whereby receptor II (p75) plays a modulatory role, being incapable of transducing signal alone [1,3—5]. Its probable role consists of enhancing the p55 signal and increasing ligand—receptor adhesion [1,4,5]. Bazzoni et al. [6] distinguish between apoptotic activity of receptor I and proliferative of receptor II. However Olsson et al. [7] hypothesize, that both receptors could be agonists and antagonists depending on their concentrations. Thus the expressions and concentrations of TNFα and receptors p55 and p75 are not determining the final effects of this complex, but their internal proportions [6]. The biological activity of TNFα depends on which of its receptors is activated.

Receptors are molecules that dissociate from cell surface, becoming the source of free molecules in blood. Serum p55 and p75 oppose TNFα activity, because they interact with TNFα in the same manner as if bound to the cell surface. Precise interaction between these three factors and significance of these interactions are still unclear and the subject of few studies. Some qualitative data are not clearly followed by quantitative studies. In a few studies it has been suggested, that there are changes in p55 and p75 concentrations on cell surfaces as well as serum levels in patients with benign and malignant ovarian tumors [8—10].

The aim of our study was to evaluate serum concentrations of p55 and p75 receptors in patients with ovarian cancer and healthy controls. Special attention was paid to p55 and p75 ratio and correlations with the disease.

2. Material and methods

The prospective study included all 51 patients consecutively treated surgically because of ovarian cancer in Department of Mother's and Child's Health and Department of Gynecologic Surgery, Poznan University of Medical Sciences, Poland between 2000 and 2003. The preoperative diagnosis was based on gynecologic examination with transvaginal ultrasound (7.5 MHz, Aloka SSD5000, Japan). The morphological score according to Ferrazzi et al. [11] and the Tumor Volume Index (TVI=0.523×A×B×C) were estimated in an ultrasound examination. Material was verified by postoperative pathological examination, with histological type, staging according to the FIGO (International Federation of Gynecology and Obstetrics) and grading (G) of malignant tumors. Preoperatively every patient had blood collected, centrifuged for 5 min at 3000 rpm. Serum was frozen and kept in −70 °C until whole material completed. The concentrations of TNFα, p55 and p75 were assayed with commercially available kits (Quantakine, R and D Systems, USA) in duplicate. The extinction was read on Dynex MRX Endpoint 1.33 (UK). According to the manufacturer the sensitivity of the p55 and p75 tests were 3.0 pg/ml and 1.0 pg/ml respectively. The intraassay precision did not exceed 8.2%. The cut-off values for p55, p75 and their ratio were estimated on Receiver Operating Characteristic curve (ROC) in the point of maximum sum of sensitivity and specificity. The CA-125 concentrations were estimated on Axsym2000 (Abbot Lab, USA), with the reference cut-off level 35 U/ml, as also used in our departments in clinical practice.

The control group consisted of 16 patients, examined according to the same protocol and additionally by internist. They did not report any chronic disease in anamnesis and had multiple laboratory tests to exclude current disease (blood morphology, CRP, AlAT, AspAT). Gynecological examination with ultrasound yielded no abnormalities. Among patients with ovarian cancer 14 were FIGO stage I, 1 patient stage II, 29 patients stage III and 7 stage IV. In postoperative histology 25 cancers were serous, 8 mucous, 8 solid, 5 endometrioid, 3 clear cell and 2 non-differentiated.

Statistical analysis was performed using SigmaStat v2.0 (Jandel Corp, USA). Differences in mean values were analyzed with the Mann—Whitney test. We also estimated the area under the ROC curve with methodology and software according to Metz et al. (ROCkit v0.9) [12]. The