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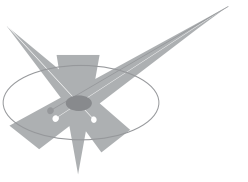

Original Paper

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Effects of active form of EGFR on disease-free survival in ovarian cancer women

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background Standard procedure in cases of ovarian cancer includes surgical treatment and complementary chemotherapy based on taxanes and platinum compounds. The results of such a procedure in advanced forms of cancer are still unsatisfactory. More accurate determination of the duration of remission with cancer patients is possible through the identification of prognostic factors. Currently adopted and extensively used prognostic factors include, among others, the age of the patient at the moment of the disease being diagnosed, the degree of clinical advancement, the size of the tumour remaining after surgery, the histological type of the neoplasm, and the volume of fluid in the peritoneal cavity. Among neoplasm markers the greatest importance is attributed to the CA 125 antigen, but continued efforts are being made in the search for new, more specific and sensitive markers.

Aim The objective of the study presented herein was estimation of the prognostic significance of the active form of EGFR in the serum of women with ovarian cancer in relation to their disease-free survival time.

Materials/Methods The study was performed on 100 women treated for ovarian cancer in the course of four years. The concentration of the active form of EGFR was determined in the blood serum, prior to treatment, using commercial immunoenzymatic sets. Disease-free survival was defined as the time elapsed from the completion of complementary first-line chemotherapy till the appearance of clinical and/or biochemical (CA 125>30 U/ml) symptoms of relapse of the neoplastic disease.

Results The concentration of the active form of EGFR fell within the range of 0.093–0.475 fmol/ml and did not show statistical significance with relation to disease-free time: the duration of the remission period was similar in patients with low as well as with high concentration of the active form of that receptor.

Conclusions Examination of concentration of the active form of EGFR in blood serum prior to surgery does not display prognostic significance for prediction of the length of the period of remission or of disease-free survival.

Key words **active form of EGFR • ovarian cancer • prognostic factors • disease-free survival**

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Background

Ovarian cancer is one of the most frequent malignant tumours in the female population. It is responsible for approximately a third of the total incidence of malignancies of women. In spite of continued improvement and advances in image-based diagnostics, in 75% of cases it is still diagnosed when in advanced form. At present, the probability of survival for 5 years from the moment the disease has been diagnosed does not exceed 46% [1], with an average of about 20–30%. Standard procedure with ovarian cancer includes surgical treatment and complementary chemotherapy based on taxanes and platinum compounds. However, therapeutic effects in advanced forms of the disease are still unsatisfactory. First-line chemotherapy, administered according to the standard sequence, six cycles at three-week intervals, leads to regression of advanced ovarian cancer in over 80% of cases, and in 40–60% the regression is total. Nevertheless, the average disease-free survival time with such patients is relatively short – the median of time free of progression is 18 months. In most patients a relapse of the disease occurs [2]. The limited effectiveness of standard chemotherapy is caused by the occurrence or development of ovarian cancer resistance to the cytostatic agents applied [3].

Cellular factors that determine the appearance of resistance to the effect of cytostatic agents include, among others, membrane receptors related to tyrosine kinase, located on the surface of ovarian cancer cells, such as the epidermal growth factor receptor EGFR. It occurs in the majority of normal cells of the human organism [4]. In the course of activation of EGFR there takes place the joining of a ligand to the extracellular domain of the receptor, followed by the formation of a dimer with participation of a second EGFR (homodimerization) or another receptor from the family of human epidermal receptors, HER, e.g. HER2/*neu* (heterodimerization), the process ending with the activation of tyrosine kinase included in the EGFR [5]. Activated tyrosine kinase catalyses phosphorylation of cytoplasmic proteins, triggering a cascade of intracellular reactions causing the growth and diversification of cells [5]. Activation of EGFR is manifested in the phosphorylation of tyrosine radicals of C-end fragment of the receptor [6]. Detection of phosphotyrosine in EGFR is the essence of immunochemical methods used for qualitative and quantitative estimation of the active form of EGFR in body fluids and tissues. Studies *in vitro* demonstrated also a relation between excessive expression of that receptor and activation of cascade of signals leading to inhibition of programmed death of cells – apoptosis [7,8]. Disturbance in the regulation of EGFR is observed in solid neoplasms, such as that of the large intestine or ovarian cancer.

Currently accepted and extensively employed prognostic factors include the age of the patient at the moment the disease is diagnosed, degree of clinical development, size of the tumour remaining after surgery, histological type of the neoplasm, and volume of fluid in the peritoneal cavity. Among neoplasm markers the greatest importance is attributed to the CA 125 antigen, but continued efforts are being made in the search for new, more specific and sensitive markers.

Aim

The objective of the study was estimation of the concentration of the active form of EGF in blood serum taken prior to surgery from women with ovarian cancer in relation to disease-free survival.

Materials and Methods

The study was performed on a group of 100 women aged 30 to 77 (median 52 years) treated for ovarian cancer at the 1st Chair and Department of Gynaecology, Medical University of Lublin. Following surgery, all the patients were subjected to complementary chemotherapy based on paclitaxel and cisplatin. Cytostatic agents were

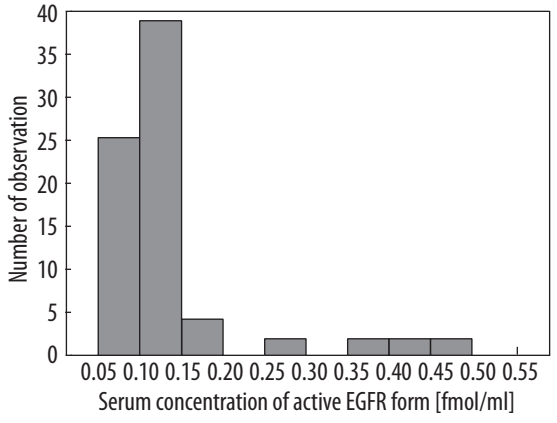

Figure 1. Serum concentration of active EGFR form in our study group.

administered every 21 days, in 6 runs, in accordance with the valid dosage schematics: paclitaxel 135mg/m^2 and cisplatin 75mg/m^2. The degree of clinical advancement of the disease was estimated following the FIGO classification [9]. Concentration of the CA 125 antigen, determined in the patients' blood serum after surgery with the enzyme-immunofluorescence method (ELFA), fell within the range from 3.3 to 5730U/ml (normal range: 0–35U/ml). The mean value of CA 125 concentration was 350.8U/ml, with a median of 27.8U/ml. Histopathology analysis of post-surgery material showed 47 cases of serum cancer, 28 cases of mucinous cancer, and 25 cases of endometrioid cancer. Disease-free survival was defined as the time elapsed from documented complete remission to the appearance of clinical (estimated by means of clinical examination of image-based examination) and/or biochemical (increased concentration of CA 125 antigen in blood serum above standard levels) symptoms of neoplastic disease relapse.

Concentration of the active form of EGFR was estimated by examining blood serum taken prior to surgery. Concentration of the active form of the EGF receptor was determined using the human Active EGF Receptor ELISA (Bender MedSystems) set with measurement sensitivity of 0.078fmol/ml. Immunoenzymatic analysis was performed in accordance with the instructions provided with the set. The analytical procedure comprised the following stages: dilution of samples and standard prior to determinations, incubation, coupling with secondary mice antibodies coupled with horseradish peroxidase, repeated incubation, enzymatic reaction, reading of absorbance and calculation of results based on the calibration curve. Statistical analysis was made using R mathematical software with Design and Hmisc libraries covered by the Public Domain Licence.

Results

Concentration of the active form of EGFR fell within the range from 0.093 to 0.475fmol/ml. The median was 0.105 fmol/ml, with RH skewness of results. The median was used for the division of the studied group of patients into those with low (<0.105fmol/ml) and high (⩾0.105fmol/ml) concentration of active form of EGFR in the blood serum (Figure 1).

Concentration of the active form of EGFR in blood serum of ovarian cancer patients did not reveal significant differences related to the age of the patients, level of clinical advancement, histological type of the neoplasm, degree of its diversification, concentration of CA 125 antigen, or size of tumour after surgery.

Post-operative treatment of ovarian cancer combined with complementary chemotherapy permitted total remission of the disease in 84 patients (84%). During the period of observation that ended on 31st December, 2004, from among the 84 patients with complete remission a relapse of the disease was recorded in 32 patients (38.1%). In the case of 52 patients (61.9%) no relapse of the disease occurred by the end of the observation period. Data on the time elapsed between the end of treatment and end of the observation period in that group of patients were considered as sheared observations. The mean disease-free survival, calculated with the Kaplan-Meier estimation method based on complete and sheared observations, was 36.2 months (95% interval of confidence: 31.2–41.2 months).

Concentration of the active form of EGFR in blood serum did not show any statistically significant relation with the duration of disease-free survival – the duration of remission was similar in patients with low and high concentrations of that form of the receptor (p=0.384) (Table 1, Figure 2).

Discussion

Study and recognition of new prognostic factors permits more profound understanding of the nature of the pathological process and development of new methods of treatment of neoplastic

Table 1. Disease-free survival (in months) in relation to serum concentration of active EGFR form. The results are presented as mean ($\bar{x}$) ± standard deviation (SE) and range. Serum concentration of active EGFR form was not statistically correlated with disease-free survival ($p>0.05$).

Active EGFR form serum concentration	Disease-free survival (in months)		p
	$\bar{x}$±SE	Range	
Low	36.1±3.5	1–48	0.3843
High	33.1±3.9	3–51	

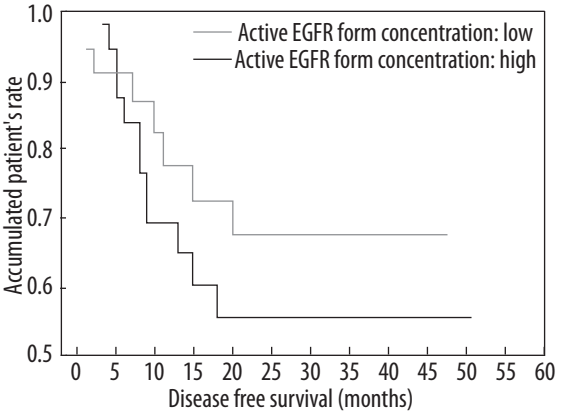

Figure 2. Disease-free survival (in months) in relation to serum concentration of active EGFR form.

diseases. Mammary cancer may be an example of this. The discovery of molecular prognostic factors, such as the oestrogen receptor or the HER 2 receptor, led to a change in the tactics of mammary cancer treatment, and to the development of a new drug – the monoclonal antibody blocking the HER 2 receptor – Herceptine [10,11]. Knowledge of new prognostic factors is also highly significant in making important clinical decisions concerning the treatment and the manner of informing a patient with cancer, or her family. Estimation of the concentration of the active form of EGFR in blood serum of patients prior to treatment allows one to find out whether there is any possibility of obtaining valuable prognostic information before undertaking surgery aimed at reducing the mass of the tumour that is the source of the active form of EGFR.

Determination of the concentration of EGFR in blood serum was the subject of studies by Baron et al., who dealt with estimations of the level of EGFR as a potential marker of ovarian cancer that could be potentially used in the diagnostic process [12,13]. Those authors observed the occurrence of low concentrations of EGFR in ovarian cancer patients. The studies published by Baron et al., however, are concerned with the occurrence of the soluble form of EGFR that constitutes the extracellular domain of the receptor, released from the surface of cells. The study of the concentration of the active form of EGFR becomes possible when using a set in which the primary anti-EGFR antibodies flatten the microplate and bind EGFR during the preliminary incubation, while antibodies reacting with areas of the receptor that are rich in phosphotyrosine are employed only at the second stage of the treatment. The active form of EGFR was present in each serum sample tested. Its concentration assumed values within the range from 0.093 to 0.475fmol/ml. The concentration did not depend on the examined clinical and histological features of the ovarian cancer, nor did it display any significant prognostic value in any of the models analysed. The analyses performed did not confirm pre-operative effectiveness of the active form of the receptor for EGF with respect to the prediction of disease-free survival of ovarian cancer patients. Examination of concentration of the active form of EGFR in blood serum prior to surgery does not display prognostic significance for the prediction of the length of the period of remission or of disease-free survival in ovarian cancer women.

Prediction of disease-free survival in ovarian cancer patients is a complex clinical problem. The use of accepted prognostic factors, such the patient's age, degree of clinical advancement of the disease, size of tumour after surgery, presence of ascites in the peritoneal cavity, type and degree of clinical advancement and concentration of CA 125, involves an excessive percentage of erroneous predictions. The necessity of searching for new molecular factors with prognostic significance will permit an increase in the number of correct predictions and may be conducive to the implementation of modern therapeutic methods of ovarian cancer treatment, based on the application of monoclonal antibodies.

Conclusions

Examination of concentration of the active form of EGFR in blood serum prior to surgery did not display any significance for prediction of the length of disease-free survival for ovarian cancer patients.

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