Effect of oxyprogesterone caproate, tamoxifen and their combination on the level of steroid hormone receptors in the tumor, and some parameters of the reproductive system in patients with endometrial cancer

A. S. VISHNEVSKY - J. A. SHTOFMAKHER - J. V. BOKHMAN
E. V. TSYRLINA - J. F. BOBROV - O. F. CHEPICK - D. F. SOFRONIY

Summary: The results of preoperative use of oxyprogesterone caproate (OPC), Tamoxifen and their combination in 165 patients suffering from primary endometrial carcinoma are presented. It was shown that Tamoxifen was able to increase concentrations cytoplasmatic receptors to progesterone in the tumor. The incidence of specific hormonal pathomorphosis in the tissue of the tumor in patients who received a combination of OPC and Tamoxifen was significantly higher (80% of cases) as compared to the separate use of OPC (60%) or Tamoxifen (57%).

The possibilities for the improvement of surgical and irradiation methods of endometrial carcinoma treatment are almost exhausted now, so there is little hope of significant improvement in survival levels as a result of modifying these therapeutic modalities.

In this clinical situation special attention should be paid to improving adjuvant hormone therapy for endometrial carcinoma patients. This therapeutic approach, for instance, prolonged administration of progestagens in remission, has made it possible to increase the five-year survival rate by 12-15% as compared to that for patients who have received surgical or combined therapy without hormone therapy [1].

One of the basic limitations to full realisation of the antitumor effect of progestinotherapy is tumor resistance to hormonal influence. Experimental and clinical data obtained with Tamoxifen therapy of breast and endometrial cancer showed that this drug had some estrogenic effects parallel to antitumor action [2]. In particular, Tamoxifen was able to increase the synthesis of cytoplasmatic receptors of progesterone in the tissue of the tumor in endometrial carcinoma [3].

These considerations gave us reason for the use of a combination of Tamoxifen and oxyprogesterone caproate (OPC) in order to increase the sensitivity of endometrial cancer to progestagen therapy.

Petrov Research Institute of Oncologoy, Leningrad (USSR)

Table 1. – *The influence of Tamoxifen on some parameters of the reproductive system in endometrial carcinoma patients (38).*

Period of investigation	FSH (un/L)	LH (un/L)	Prolactin (mun/L)	Estradiol (pmol/L)	KPI (%)
Before treatment	34.0±3.3	42.5±5.1	236±32	77.8±19.4	33±4
By completion of hormonotherapy	29.9±3.4	34.7±6.1	237±45	66.4±14.7	54±3
P (t-test)	>0.1	>0.1	n.s.	>0.1	<0.01

The aim of this paper is to specify, in comparative analysis, the influence of Tamoxifen, OPC and their combination on some parameters of reproductive homeostasis and the level of steroid hormone receptors in the tumor in endometrial carcinoma patients. This analysis might be useful in developing methods of overcoming endometrial cancer resistance to hormonal therapy.

MATERIAL AND METHODS

This paper deals with the results of preoperative hormonal treatment of 167 patients with primary endometrial carcinoma, Stage I-III (FIGO), mean age 56.9 years. Hormone therapy was administered to all the patients for 21 days before surgery: 46 patients received OPC (total dose - 10.5 gr), 49 received Tamoxifen (1.26 gr orally) and 72 received a combination of Tamoxifen (1.26 gr) and OPC (10.5 gr).

After completion of the hormone therapy, surgical intervention (a simple hysterectomy or an extended one) was carried out. Blood samples and neoplastic tissues were analysed. The methods of preservation and receptorial and hormone assays have already been described [4].

The karyopyknotic index (KPI) reflecting estrogenic level was calculated in stained vaginal smears as the percentage ratio of superficial cells with pyknosis of their nuclei to the general amount of superficial epithelial cells.

The antitumor effect of preoperative hormone therapy was estimated by a change in the histological structure of the tumor determined in operative samples ("hormonal pathomorphosis"). Hormonal pathomorphosis consisted of the following sequence of changes in the histological structure of endometrial cancer under hormone therapy: decrease in proliferative activity, increase in the structural and functional differentiation, active secretion, secretory exhaustion, atrophic changes which result in the necrosis of the tumor and its complete or partial regression.

RESULTS AND DISCUSSION

As Table 1 shows, Tamoxifen had not decreased the secretion of FSH, LH, prolactin and estradiol by the moment of completion of hormone therapy. There was a pronounced estrogenic effect of Tamoxifen on the vaginal epithelium reflected in increasing KPI. The " Central " effect OPC on secretion of FSH, LH and estradiol essentially different from the action of Tamoxifen. Administration of OPC resulted in significant depression of secretion of FSH, LH and estradiol, which was determined by the completion of hormone therapy by 69.6%, 79,2% and 58.5% respectively of the basal level. Against the background of this decreased

Table 2. – *The influence of combined hormone therapy (Tamoxifen and Oxyprogesterone caproate) on some parameters of reproductive system in endometrial carcinoma patients (n = 72).*

Period of investigation	FSH (un/L)	LH (un/L)	Prolactin (mun/L)	Estradiol (pmol/L)	KPI (%)
Before treatment	50.6±4.4	43.7±4.3	334±58	285.5±38	35±2
By completion of hormonotherapy	20.2±2.6	45.3±32	332±76	123.1±11.5	27±2
P (t-test)	=0.001	n.s.	n.s.	=0.01	+0.01

Table 3. – *Dynamics of change of estradiol and progesterone cytoplasmatic receptors in endometrial carcinoma effected by Tamoxifen therapy depending on estradiol-receptors basal level.*

Basal level ER (fmol/mg protein)	ER (fmol/mg protein)		P	PR (fmol/mg protein)		P
	Before treatment	After treatment		Before treatment	After treatment	
8 (n = 19)	2.3±0.5	16.0±2.9	<0.01	45.3±20.4	178.9±36.5	<0.01
40 (n = 15)	21.1±3.0	8.5±1.5	<0.01	20.2±8.7	173.6±58.7	<0.02
40	122.7±28.8	33.2±13.5	<0.02	84.5±28.2	323.9±76.0	<0.01

level of the hormones, there was no essential change of secretion of prolactin under OPC-hormone therapy. The antiestrogenic effect of OPC on the tissue-target of the reproductive system was revealed by the essential decrease of KPI (60.4% below the basal level) by the completion of hormone therapy.

From this comparison it can be concluded that OPC by itself, apart from the isolated administration of Tamoxifen, possesses an expressed antigonadotropic effect resulting in decrease of estradiol level in the blood. This central effect of OPC is combined with its direct antiestrogen influence on the target-tissue, namely the decrease of KPI. It is necessary to emphasise that this antiestrogenic effect of OPC was sustained when OPC was used in combination with Tamoxifen, exceeding the estrogenic effect of the latter on the vaginal epithelium (Table 2).

Administration of combined OPC-Tamoxifen therapy resulted in the decrease of gonadotropin and estradiol secretion, similar to the effect of OPC-isolated hormone therapy. A slight decrease of KPI was observed (Table 2).

Computerized multifactorial analysis did not show any significant correlation between changes of gonadotropic secretion during all kinds of hormone therapy on the one hand, and the incidence of hormonal pathomorphosis in the tumor on the other. But there was a positive correlation between the estrogenic type of vaginal smear (KPI>20%) and hormonal pathomorphosis resulted from OPC and OPC+Tamoxifen hormone therapy. The influence of Tamoxifen on cytoplasmatic oestradiol receptor (ER) in the tumor was different and depended on its basal level. Thus Tamoxifen increased the ER level 7 times if its basal level was low (<8.0 fmol/mg protein) and, on the contrary, decreased the ER level if its basal concentration was high (>40.0 fmol/mg protein). Table 3. As can be see in Table 3, there was a marked increase of cytoplasmatic progesterone receptor (PR) concentrations in the tumor effected by Tamoxifen hormone therapy. Stimulation

Table 4. – *Dynamics of the change of estradiol and progesterone cytoplosmatic receptors in endometrial carcinooma effected by oxyprogesterone caproate and combined hormone therapy with Tamoxifen and oxyprogesterone caproate.*

Period of investigation	OPC-therapy (n = 46)		OPC+Tamoxifen therapy (n = 72)			
	ER (fmol/mg protein)	PR (fmol/mg protein)	ER (fmol/mg protein) ⩽10	⩾10	PR (fmol/mg protein) ⩽20	⩾20
Before treatment	22.4±6.4	27.7±7.9	8.2±0.5	54.8±14.6	11.8±1.1	67.7±14.0
After treatment	12.2±3.3	7.7±1.4	6.7±0.6	46.0±12.5	20.5±2.6	44.1±18.0
Wilkoxon's test	<0.05	<0.01	>0.05	=0.05	=0.01	<0.05

of PR in the tumor induced by Tamoxifen was more pronounced in those patients who had a high level of ER. This fact suggests that the stimulating effect of Tamoxifen on PR-synthesis was realised through the ER. At the same time it can be suggested that Tamoxifen, by stimulating cytoplasmatic receptors to progesterone (PR) in the tumor tissue, may increase the sensitivity of the tumor to progestin hormone therapy (Table 3). Actually, the incidence of hormonal pathomorphosis in the group of patients who received the combination of OPC and Tamoxifen was significantly higher (80.5% of cases) than in patients who received OPC (60.8%) or Tamoxifen (57.8%) only $\chi^2=7.6$. $P=0.01$.

The dynamics of change in the steroid receptor levels in the tumor during OPC-therapy and combined hormone therapy is presented in Table 4. As this table shows, a significant decrease of both PR– and ER levels in the tumor effected by OPC-therapy was observed. This effect of OPC, peculiar to many progestagens, might be explained by a decrease of intracellular concentrations of estradiol as a result of induction by progestogen of 17 beta-estradiol dehydrogenatse ([5]). The decrease of intracellular concentrations of estradiol results, in its turn, in lowering both ER and PR levels, whose synthesis was controlled by estradiol.

In the case of combined hormone therapy a dual effect of this scheme on the dynamic of change PR-levels in the tumor was shown (Table 4). If the basal level of PR was low (<20 fmol/mg protein) there was a significant increase of it by the moment of completion of the hormone therapy, and, on the contrary, the high basal level of PR (>20 fmol/mg protein) was decreased by the completion of combined hormone therapy. In our opinion it is a remarkable fact, indicating the capacity of Tamoxifen to keep its stimulative estrogenic action on the PR synthesis even in combination with OPC therapy.

On considering these data one can conclude that for all patients with endometrial carcinoma who have poor prognosis and/or show clinical and morphological signs of resistance to hormone therapy (hypoestrogenia, low level of PR, decrease of morphologic grade of the tumor) treatment by a combination of progestogen and Tamoxifen would be preferable in remission for a long period (up to 3 years) to prevent recurrence of the disease.

REFERENCES

1) Bokhman I. V.: *Gynecol. Oncol.*, *11*, 371, 1981.
2) Billeiet G., De Herzog R., Bonte J. *et al.*: *Gynecol. Oncol.*, *14*, 33, 1982.
3) Bonte J., Ide P., Billiet G.: *Gynecol. Oncol.*, *11*, 140, 1981.
4) Tsyrlina E. *et al.*: *Vopr. Oncol.*, *35*, 675, 1989.
5) Schmidt-Gollwitzer M.: *Endometrial Cancer.* Ed. Brush M. G. *et al.*, p. 227-241, London, 1978.