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Original Research Article

The development of resistance to tamoxifen in patients with breast cancer: our experience

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ABSTRACT

Background: The study used data from medical and counselling of patients who were diagnosed with hormone-dependent breast cancer. Aim: The objective of the paper is to identify within a group of patients diagnosed with hormone sensitive breast cancer and those who have received adjuvant tamoxifen, and then to isolate the patients with whom the therapeutic effect of tamoxifen stopped (resistance to tamoxifen).
Methods: The study analyzed 153 patients in the period from 2005 to 2011, at the Public Health Institution Hospital, Sveti Vračevi" in Bijeljina. Resistance to tamoxifen was developed by 60 patients (39.2%) and 93 patients (60.8%) did not develop resistance to it.
Results: More common emergence of resistance is in the premenopausal group of patients ($p<0.001$). Statistically significant difference in frequency of resistance to tamoxifen was observed in the group of patients with ER-/PrR+ status of steroid receptors ($p<0.001$). In relation to HER-2 status of diagnosed cancer, a statistically significant difference in frequency of resistance emergence during tamoxifen therapy in patients with HER2-positive status ($p<0.001$) was observed. We found that there is a statistically significant difference between patients with metastatic in lymph nodes compared to patients who had no metastases in lymph nodes ($X^2=39.494$; $p<0.001$).
Conclusions: The analysis of menopausal status of patients, status of ER/PgR receptors status, HER-2 status of diagnosed cancer and status of lymph nodes trying to sort out the parameters on the basis of which a group of patients who can be expected to develop resistance to tamoxifen could be differentiated.

Keywords: Breast cancer, Tamoxifen, Resistance

INTRODUCTION

Tamoxifen competitively binds to estrogen receptors (ER) in breast cancer cells and other target tissues, building a nuclear complex that decreases the synthesis of DNA and prevents the effects of estrogen.

Tamoxifen have an agonist and antagonist activity. In breast cancer tumor cells an agonistic activity is demonstrated when intracellular level of tamoxifen is low.[1] Low levels stimulate the synthesis of P-glycoprotein, and high ones inhibit this synthesis. Resistance can be developed when the reduced

absorption of tamoxifen increased the value of P glycopotein. Increased expression of antiestrogen binding sites (AEBS) that bind tamoxifen with similar affinity as ER can reduce the intracellular level of tamoxifen thus making the cells resistant to tamoxifen therapy. Increased expression of AEBS can be resistance mechanism to tamoxifen.[2]

The causes of resistance during treatment of breast cancer patients may be; Changes in the influx and metabolism of tamoxifen, loss of expression of ER3, decreased expression of ER, expression of mutant or variant forms of ER, ER is intact, but cofactor is lost et al.[3]

Mechanisms of resistance to tamoxifen

Primary resistance to tamoxifen, ER mutations cause the development of resistance to tamoxifen, Saturation of ER with tamoxifen-if limited-leads to resistance and increased metabolism of tamoxifen in agonist metabolites is a possible reason for resistance.[4]

Biology of estrogen receptors cannot be analyzed in isolation from other intracellular signaling pathways. In recent years, it was found that there exist multiple regulatory interactions among ER, growth factors and other kinases of signaling pathways. Therefore, the way of action of growth factors can regulate and stimulate the growth independently of ER, or can communicate through a crosslink reaction with ER. Thus, it monitors cell growth and resistance mode.[5]

The objective of the paper is to identify within a group of patients diagnosed with hormone sensitive breast cancer and those who have received adjuvant tamoxifen, and then to isolate the patients with whom the therapeutic effect of tamoxifen stopped (resistance to tamoxifen) and with whom treatment was continued with another drug or method. The analysis of menopausal status of patients, status of ER/PgR receptors, HER-2 status of diagnosed cancer and status of lymph nodes is trying to sort out the parameters on the basis of which a group of patients who can be expected to develop resistance to tamoxifen could be differentiated.[6]

METHODS

The study used data from medical and counseling of patients who were diagnosed, in the period from 2005 to 2011, at the Public Health Institution Hospital, Sveti Vračevi" in Bijeljina, with hormone-dependent breast cancer. There were 153 patients who were, after surgical treatment (sparing or radical surgery with mandatory ipsilateral axillary dissection), treated with adjuvant hormonal therapy - tamoxifen tablets 0.01 g in mornings and evenings, as the only postoperative therapy, or in combination with other forms of treatment-chemotherapy or radiotherapy. From this group, a subgroup of patients was set aside, who during the application of the hormone therapy developed resistance ie. occurrence of relapse of illness (local recurrence or metastatic disease), and such patients were presented again to Oncology specialist consultants in order to have their therapies changed. From a total of 60 patients who were observed relapsed disease, 7 patients had local recurrence and 53 metastatic diseases.

RESULTS

The study analyzed 153 patients, of which the resistance to tamoxifen was developed by 60 patients (39.2%), while 93 patients (60.8%) did not develop resistance to it. The average age of patients was 56.4±10.4 years, with a median of 55. From the total number of patients, 62 have pre-menopausal status (40.5%), while 91 of the patients (59.5%) had postmenopausal status. Invasive ductal carcinoma was present in 95 patients (62.1%), invasive lobular carcinoma in 46 patients (30.1%), and less common histological types of breast cancer were present in 12 patients (7.8%). 93 patients (60.8%) had metastasis in lymph nodes, while 60 patients (39.2%) had no metastasis in lymph nodes. 123 patients (80.4%) had radical surgery, while 30 patients (19.6%) had a sparing one. 82 patients (53.6%) were treated by postoperative radiotherapy, while 71 patients (46.4%) were not treated in this way. Adjuvant chemotherapy was received by 121 patients (79.1%), while 32 patients (20.9%) were not treated in this way.

The distribution of patients as per estrogen/progesterone receptor status (Er/PgR) is presented in Table 1.

55 patients (35.9%) had positive HER-2 and 98 patients (64.1%) had negative one.

Table 1: The distribution of patients as per Er/PgR status.

Group	N	%
Er+/PgR-	11	7.2
Er+/PgR+	120	78.4
Er-/PgR+	22	14.4
Total	153	100.0

Er+ - estrogen positive receptors, PgR+ - progesterone positive receptors, Er- -estrogen negative receptors, PgR- - progesterone negative receptors

Resistance to tamoxifen

The development of resistance to tamoxifen was analyzed by comparing the patients in relation to menopausal status (pre and post-menopausal status) are presented in Table 2.

There was a statistically significant difference in the development of resistance during treatment with tamoxifen among patients with premenopausal and postmenopausal status. More common the development of resistance is in the premenopausal group of patients ($X^2 = 12.992$, $p<0.001$). We analyzed the development of

resistance to tamoxifen and compared the patient in relation to the status of ER/PgR receptors are presented in Table 3.

Table 2: The emergence of resistance to tamoxifen in relation to menopausal status.

			Resistance		Total
			No	Yes	
Menopausal status	Pre	N	27	35	62
		%	43.5%	56.5%	100.0%
	Post	N	66	25	91
		%	72.5%	27.5%	100.0%
Total		N	93	60	153
		%	60.8%	39.2%	100.0%

Table 3: The emergence of resistance to tamoxifen in relation to ER/PgR status.

Er+/-			Resistance		Total
			No	Yes	
Status ER/PgR	Er+/PgR-	N	8	3	11
		%	72.7%	27.3%	100.0%
	Er+/PgR+	N	83	37	120
		%	69.2%	30.8%	100.0%
	Er-/PgR+	N	2	20	22
		%	9.1%	90.9%	100.0%
Total		N	93	60	153
		%	60.8%	39.2%	100.0%

Er+ - estrogen positive receptors, PgR+ - progesterone positive receptors, Er- -estrogern negative receptors, PgR- - progesterone negative receptors

In relation to the status of ER/PgR receptors of diagnosed breast cancer statistically significant difference in frequency of resistance to tamoxifen was observed in the group of patients with ER-/PrR+ status of steroid receptors (X^2 = 28.858; p <0.001).

We analyzed the development of resistance to tamoxifen comparing patients in relation to the status of HER-2 receptor are presented in Table 4.

In relation to HER-2 status of diagnosed cancer, a statistically significant difference in frequency of resistance the development during tamoxifen therapy in patients with HER2-positive status (X^2=59.919; p<0.001) was observed.

The development of resistance to tamoxifen was analyzed by comparing the patients in relation to the presence of metastases in lymph nodes are presented in Table 5.

Analyzing the development of resistance to tamoxifen we found that there is a statistically significant difference between patients with metastatic in lymph nodes compared to patients who had no metastases in lymph nodes (X2=39.494; p<0.001).

Table 4: The emergence of resistance to tamoxifen in relation to HER-2 status.

			Resistance		Total
			No	Yes	
HER-2 status	-	N	82	16	98
		%	83.7%	16.3%	100.0%
	+	N	11	44	55
		%	20.0%	80.0%	100.0%
Total		N	93	60	153
		%	60.8%	39.2%	100.0%

HER-2- human epidermal growth factor receptor 2

Table 5: The emergence of resistance to tamoxifen in relation to the presence of metastases in lymph nodes.

			Resistance		Total
			No	Yes	
Lymph node metastases	-	N	55	5	60
		%	91.7%	8.3%	100.0%
	+	N	38	55	93
		%	40.9%	59.1%	100.0%
Total		N	93	60	153
		%	60.8%	39.2%	100.0%

The development of resistance to Tamoxifen was analyzed by comparing patients with histological types of breast cancer are presented in Table 6.

Table 6: The emergence of resistance to tamoxifen in relation to the histological type of tumor.

			Resistance		Total
			No	Yes	
Histological type of tumor	Ductal	N	62	33	95
		%	65.3%	34.7%	100.0%
	Lobular	N	26	20	46
		%	56.5%	43.5%	100.0%
	Other	N	5	7	12
		%	41.7%	58.3%	100.0%
Total		N	93	60	153
		%	60.8%	39.2%	100.0%

In relation to the histological type of breast cancer there was no statistically significant difference in frequency of resistance during treatment with tamoxifen (X^2=2.990; p=0.224).

DISCUSSION

The basic premise of this study is that there are some predictive factors that could indicate the possibility of resistance during treatment with tamoxifen of hormone-dependent breast cancer.

As possible factors which might be associated with the development of resistance to tamoxifen the following were considered: menopausal status, ER/PgR status,

status of HER-2 receptor, the presence of lymph node metastases and the histological type of breast cancer.

All patients included in the study had immunohistochemistry confirmed positive SR status (ER+/PrR+; ER+/PrR-; ER-/PrR+).

The study included a total of 153 patients. Resistance to the application of tamoxifen, in terms of occurrence of relapse (local recurrence or metastatic disease), has been developed with 39.2%, while the occurrence of resistance was not found with 60.8% of patients in the interval of 5 years.

From a total of 60 patients with developed resistance to tamoxifen, local recurrence was observed with 7 patients while 53 of them had metastatic disease.

The average age of patients in the study was 56.4 years. In the study of Hefti average age of patients at the time of diagnosing breast cancer is 56 years, 16% under 40 years of age, 24% were 40-49 years of age.[7]

Menopausal status was determined by the following criteria - premenopausal status was given to the patients with regular menstrual cycles or to the patients who confirmed the absence of a menstrual cycle up to 6 months prior to diagnosing breast cancer. All others were considered postmenopausal. After statistical analysis, it was found that there is a significant difference between patients with premenopausal and postmenopausal status as to the frequency of resistance to tamoxifen (X^2=12.992; p<0.001). More frequent phenomenon of resistance is found among premenopausal women with breast cancer treated with tamoxifen. The literature refers to the similar conclusions by Dubsky, Ellis as well as Bartsch in their studies.[8-10]

International Breast Cancer Study Group (IBCSG) analyzed 314 patients suffering from breast cancer of the age <35 years, and reported that relapse or death disease occurs earlier and more frequently in premenopausal group of patients.[11]

Status of steroid receptors (SR)

The patients analyzed in this clinical study had positive SR in different combinations. Er+/PgR- status 7.2%; ER+/PgR+ status 78.4%; Er-/PgR+ status 14.4%. The development of resistance is the most common with Er/PgR+ status, while the incidence of resistance during treatment with tamoxifen is the smallest with Er+/PgR+ status (X2=28.858; p<0.001). Caldon reported similar data in their study.[12]

HER-2 status

In our clinical study we have concluded that there is statistically significant difference in the development of resistance to tamoxifen in patients who have had a positive HER-2 receptors in relation to the group of patients who had HER-2 negative receptors (X2=59.919; p<0.001). In literature, many studies confirm the same conclusions Diaz.[13]

The presence of metastases in lymph nodes

The development of resistance to tamoxifen were more frequently recorded in patients who have had lymph node metastases compared to patients who had no metastases in the lymph nodes (X^2=39.494; p<0.001). Wang registered a similar conclusion in their study.[14]

The histological type of diagnosed tumor

After statistical analysis we found that there was no statistically significant difference between patients with ductal, lobular and other patohystological types of cancer in the development of resistance to tamoxifen.

Fisher B et al. in his clinical study with 735 patients, who were diagnosed with breast cancer of various PH types, concluded that histological type of diagnosed tumor does not affect the frequency and time of the development of relapse nor the overall survival.[15,16]

CONCLUSION

The development of resistance during the application of adjuvant hormone therapy with tamoxifen 2x0.01 g tablets with patients diagnosed with hormone-dependent breast cancer is more often observed in the group of patients with premenopausal status.

In relation to the status of ER/PgR receptor diagnosed breast cancer a statistically significant difference in frequency of resistance to tamoxifen was observed in the group of patients with ER-/PrR+ status of steroid receptors.

In relation to HER 2 status diagnosed cancer, a statistically significant difference in the frequency of resistance was observed during treatment with tamoxifen with patients with HER-2 positive status.

Analyzing development of resistance to tamoxifen we found that there is a statistically significant difference between patients with metastatic in lymph nodes compared to patients who had no metastases in lymph nodes.

In relation to the histological type of breast cancer there was no statistically significant difference in frequency of the development of resistance during treatment with tamoxifen.

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