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ISSUES OF INDIVIDUALIZATION OF MEDICATION IN PATIENTS WITH BREAST CANCER

ВОПРОСЫ ИНДИВИДУАЛИЗАЦИИ ЛЕЧЕНИЯ БОЛЬНЫХ РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ

Abstract. The **purpose** of this study was to search for approaches to individualization of adjuvant chemotherapeutic treatment of breast cancer based on a study of the effectiveness of anthracycline chemotherapy regimens in various molecular biological tumor subtypes.

Materials and methods: The study included 399 patients with breast cancer stage I-III, differing in molecular biological tumor subtypes. Of these, 205 patients received chemotherapy. The criteria for determining the molecular biological tumor subtypes were consistent with the latest recommendations of St. Gallen (Goldhirsch et al., 2013). Tumors with ER and/or PR expression and low (<20%) Ki67 were classified as luminal A. Luminal B was associated with ER expression with either high Ki67 (>20%) or HER2/neu overexpression. In triple-negative cancer (TNC), there was no expression of any of the major markers, and in the HER2/neu type, only this receptor was overexpressed. Adjuvant chemotherapy (51.4% of patients) in our study was carried out according to CAF scheme (doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2, 5-fluorouracil 500 mg/m^2) or AS (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2) every 21 days. Radiation therapy was performed in 41.4% of patients, hormonal therapy in 64.9% of patients.

Results: Molecular biological subtypes of breast cancer played a decisive role in the effectiveness of chemotherapy. FAC/AC treatment was not effective in patients with luminal A type of breast cancer.

Аннотация. Целью данной работы является поиск подходов к индивидуализации адъювантного химиотерапевтического лечения рака молочной железы на основании исследования эффективности антрациклиновых схем химиотерапии при различных молекулярно-биологических подтипах опухоли.

Материалы и методы: В исследование включены 399 больных раком молочной железы I-III стадии, отличающиеся по молекулярно-биологическим подтипам опухоли. Из них 205 больных получали химиотерапию. Критерии определения молекулярно-биологических подтипов опухоли соответствовали последним рекомендациям Сан-Галлена (Goldhirsch et al., 2013). К люминальному А относили опухоли с экспрессией РЭ и/или РП и низкой (<20%) Ki67. К люминальному В относили опухоли с экспрессией РЭ, у которых были или высокий Ki67 (>20%), или гиперэкспрессия HER2/neu. При тройном-негативном раке (ТНР) нет экспрессии ни одного из основных маркеров, а при HER2/neu типе гиперэкспрессирован только этот рецептор. Адъювантная химиотерапия (51,4% больных) в нашем исследовании проводилась по схеме CAF (доксорубицин 50 мг/м^2, циклофосфан 500 мг/м^2, 5-фторурацил 500 мг/м^2) или АС (доксорубицин 60 мг/м^2, циклофосфан 600 мг/м^2) каждые 21 день. Лучевая терапия проводилась у 41,4% больных, гормонотерапия – у 64,9% больных.

Результаты: Молекулярно-биологические подтипы рака молочной железы играют определяющую роль в эффективности химиотерапии. Лечение по схеме FAC/AC оказалось не эффективным у больных с люминальным А типом рака молочной железы.

Key words: breast cancer, the effectiveness of chemotherapy, molecular biological tumor subtypes.

Ключевые слова: рак молочной железы, эффективность химиотерапии, молекулярно-биологические подтипы.

Introduction. Breast cancer (BC) is the most common cancer in women worldwide [2, 3-5, 11]. One of the main types of treatment for breast cancer is systemic chemotherapy (CT) with the inclusion of anthracyclines. However, the issue of individualization of this CT scheme is becoming more pressing with each year [2, 9, 10]. Perou C.M. et al., examining samples of breast tumors, created a classification of breast cancer, based on variations in the pattern of gene expression. This constantly improved classification is based on the characteristics of several molecular markers: estrogen receptors (ER), progesterone receptors (PR), HER2/neu expression. [6-8]

The **purpose** of this study was to search for approaches to the individualization of adjuvant chemotherapeutic treatment of breast cancer based on a study of the effectiveness of anthracycline chemotherapy regimens for various molecular biological tumor subtypes.

Materials and methods of the study

The study included 399 patients with breast cancer stage I-III. Patients received complex treatment at the departments of oncology, chemotherapy and the department of radiation therapy of Kharkiv Cancer Center and Kharkiv City Hospital No. 17 from 2010 to 2018. The characteristics of the patients are presented in Table 1. The observation time for patients ranged from 1 to 241 months (average observation period was 44.4 months).

The criteria for determining molecular biological tumor subtypes were consistent with the latest recommendations of St. Gallen (Goldhirsch et al., 2013). Tumors with ER and/or PR expression and low (<20%) Ki67 were classified as luminal A. Luminal B was associated with ER expression with either high Ki67 (> 20%) or HER2/neu overexpression. In triple-negative cancer (TNC), there was no expression of any of the major markers, and in HER2/neu type, only this receptor was overexpressed.

Table 1

Characteristics of patients

Number of patients (n)	Without chemotherapy (n=194)		Chemotherapy (n=205)	
	Number	%	Number	%
Age, years < 50 years > 50 years	46 148	23.7 76.3	94 111	45.9 54.1
Stage Stage I Stage II Stage III	36 137 21	18.6 70.1 11.3	6 100 99	2.9 48.8 48.3
ER and PR status ER/PR-positive ER/PR-negative N/A	113 50 31	58.2 25.8 15	90 62 52	41.1 30.4 28.5
HER2 status Negative Positive	49 9	84.5 15.5	82 13	86.3 13.7

Treatment. Adjuvant chemotherapy (51.4% of patients) in our study was carried out according to CAF scheme (doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2, 5-fluorouracil 500 mg/m^2) or AS (doxorubicin 60 mg/m^2, cyclophosphane 600 mg/m^2) every 21 days. Radiation therapy was performed in 41.4% of patients, hormonal therapy in 64.9% of patients.

Statistical analysis. The relapse-free survival (RFS) and overall survival (OS) were analyzed using the Kaplan-Meier method, and these indices were compared using a log-rank test. RFS was determined from the date of surgery to the date of progression. OS was calculated from the date of surgery to the last observation or death. In OS and RFS calculation the patients, excluded from observation, were censored at the time of the analysis by the date of their last visit or telephone interview. Non-parametric data, depending on the number of observations, were analyzed using the χ^2 test or Fisher's exact test. In all cases, a 95% confidence interval (95% CI) and a two-sided criterion of significance p were used, the difference was considered statistically significant at $p \leq 0.05$. Statistical analysis was performed using GraphPadPrism 5.1.

Results and discussion

Dependence of overall and relapse-free survival on various molecular biological tumor subtypes. In our sample of patients, the predominant subtype was luminal A – 36.4%, then TNC and luminal B were the most prevalent – 27.8% and 26.5%, respectively, HER2 / neu-positive subtype ranked last – 9.3 % of patients.

The highest OS was found in the luminal A subgroup – 74.1% of patients were observed without signs of disease progression for about 8 years (93 months), and the lowest in the HER2/neu-positive cancer subgroup – during the first year 50% of patients showed disease progression. In the group with TNC subtype, 34% of patients showed signs of distant metastasis during the first two years, and then this cohort of patients was observed for another 7.5 years without signs of progression. In the group with luminal B subtype, 30.1% of patients showed signs of tumor progression during the first 3.5 years (43 months), and in the next 5.5 years the mortality rate was not significant (p = 0.06).

The analysis of OS showed that patients with luminal A also had a more favorable prognosis – 84.1% of patients lived 10 years. In luminal B, 52.7% of patients lived more than 10 years, whereas only 50% of patients with HER2/neu-positive subtype were alive by the 5-year observation period. The worst OS was observed in the group with TNC-subtype – 28.3% of patients lived more than 10 years (p = 0.06). Thus, in our study, patients with luminal A phenotype had the best both OS and RFS. All major events associated with the further progression of the tumor process occurred in this group in the first 40 months, and then there was a long plateau, which in our study reached 9.5 years. The high survival rate of patients in this group may be due to hormone therapy after the completion of cytostatic treatment.

The fastest rates of progression and mortality in our study were observed among patients of the HER2/neu-positive cancer group— the first signs of progression were observed in the first year of observation, the OS was also low and was 50% by the fifth year of observation. This correlates with international studies in which these groups of patients show the worst survival rates (Mulligan et al., 2008; Dawood et al., 2011; Haque et al., 2012).

A group of patients with luminous B and HER2/neu showed comparable levels of RFS and OM, differing from the latter only in the later periods of occurrence of events. Distant metastasis in the subgroup of patients with luminal B tumor subtype

were detected in the first three years, the level of 50% OS in this subgroup was reached within 10 years.

Women with TNC also had an unfavorable prognosis. Our study showed that all cases of progression occurred in the first two years from the moment of operation, and then RFS went out on the same level and persisted for 7.5 years. The OS in this subgroup did not exceed 25%, which was 3.3 times lower than the OS in the luminal group A. Thus, we found that patients in this group also differed in their clinical outcomes: some patients progressed early and died despite treatment, and some lived without signs of progression for a long time. It is highly probable that there were unknown factors that made this group heterogeneous both clinically and at the molecular level (Mulligan et al., 2008).

Dependence of overall and relapse-free survival on medication and molecular biological tumor subtype. Patients with hormone-positive tumors with luminal A subtype who did not receive chemotherapy (87.5%) showed better RFS compared with patients who received chemotherapy (66.7%). Moreover, in the group of patients receiving chemotherapy, the first case of progression was detected 8 months after the operation, whereas in the absence of medication, the first case of progression was noted 36 months after the operation.

In the group of patients with luminal B subtype, a reverse trend was observed: in patients who did not receive chemotherapy, progression was detected after the first 3 months, while in patients who received treatment, the first signs of disease progression were recorded only after 19 months of follow-up.

In patients with TNC, regardless of chemotherapy, the first signs of distant metastasis were diagnosed early (in the first months of observation). However, in the group of patients receiving chemotherapy, after 18 months of follow-up, there were no cases of progression, while in the group that did not receive medication the last case of progression was noted after 26 months. Thus, the level of RFS in the group that did not receive chemotherapy, by the end of the observation reached 35%, and in the group of patients who received treatment it was 79%.

Assessment of the OS among patients with luminal A subtype in the first years of observation showed no significant difference between treated and untreated patients, however, as they approached 5 years of follow-up (59 months), 11% of patients who received hormone therapy but did not receive chemotherapy died due to progression. At the same time, in the group of patients who received chemotherapy in the first months after a five-year period (62 months), 20% of patients died of BC progression ($p = 0.8$).

In the group of patients with hormone-positive, HER2/neu-positive tumors (luminal B), 10% of patients who did not receive chemotherapy died after 27 months of observation, but in subsequent years of observation the rest of the cohort of these patients remained alive for 10 years term. Those patients who received chemotherapy were alive for 5 years, then the number of deaths increased, reaching 50% by 64 months, and then this group remained alive until the 10-year follow-up period ($p = 0.8$).

Given that breast cancer is a very heterogeneous disease, the effect of systemic treatment varies depending on the subgroups of patients whose tumors differ in their biological characteristics. The first such observations were made in the treatment of cytotoxic drugs estrogen-positive patients. Now, as noted by Professor G. Hortobagyi, all oncologists recognize the fact that the gain that chemotherapy patients receive from hormone-positive tumors is much more modest than that in patients with hormone-negative tumors (Hortobagyi, 2007). In our study, we found the same tendency; the survival rate in the subgroups of luminal A and TNC significantly differed depending on the chemotherapy — in the TNC group, treatment improved RFS and OS.

However, it is known that estrogen-positive tumors are also heterogeneous. This group can include both luminal A tumors that do not carry HER2/neu antigens on their surface, and luminal B, which includes hormone-positive, HER2/neu positive tumors. This group of tumors proliferates faster and is probably more chemically sensitive (IBCSG, 2002). Indeed, in our study, patients of this group (luminous B) showed greater sensitivity to chemotherapy and it had a greater effect in this group, unlike the group where patients did not receive chemotherapy. Thus, in the group with luminal B without treatment, the first relapse occurred after 3 months, and in the group with luminal A after 36 months. The results of the association of chemotherapy and survival in the group of HER2/neu-positive tumors are not presented due to the small sample size. The TNC subgroup of patients without systemic treatment progressed very quickly, but with treatment — regardless of the treatment regimen — progression occurred in the first three years (Dawood et al., 2011; Lehmann, Pietenpol, 2014).

Although, as shown in our study, adjuvant therapy prolongs the time before progression and overall survival, however, in certain subgroups of patients with BC, this type of treatment does not benefit all patients, and sometimes, perhaps, is even harmful.

Conclusions

1. Assessment of the overall and relapse-free survival of patients with breast cancer depending on the molecular biological subtypes of the tumor has shown that this dependence corresponds to the literature data: the luminal A subtype of the tumor has the most favorable course.

2. FAC/AC treatment is ineffective in patients with luminal A type of breast cancer.

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