TRIPLE NEGATIVE BREAST CANCER: CURRENT VIEW ON THE PROBLEM

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Summary. Therapy of triple negative breast cancer (TNBC) remains one of the most difficult problems of oncology. This type of BC combines biological aggressiveness and limited number of treatment modalities, and often affects young women. From great arsenal of the contemporary BC treatment methods only chemotherapy is appropriate for TNBC. Despite the great number of the dedicated to TNBC clinical studies, at present there exist no standard chemotherapy regimen for this subtype? And results of treatment remain unsatisfactory. Actively implemented in recent years principles of maximal individualization of BC therapy are unsuccessful for the triple negative type. The article presents the review of the most significant clinical studies devoted to neoadjuvant and adjuvant chemotherapy of TNBC.

Key words: triple negative breast cancer, neoadjuvant chemotherapy,. adjuvant chemotherapy.

Breast cancer (BC) in recent years, both in Ukraine and in many countries of Western Europe and North America remains the most common malignancy in women. However, analyzing the BC survival rates in the last decade, it is possible to conclude that there exists a trend towards improved outcomes of this disease. Thus, according to the SEER (Surveillance, Epidemiology and End Results) - statistical database of the National Cancer Institute (USA), 5-year survival of localized forms of BC is 83.4% - 98.4%, and for metastatic - 23.3% [9]. Such good results could be associated primarily with the achievements in BC systemic

therapy, in particular, using the strategy of maximal individualization of therapy. BC is a heterogeneous group of tumors. According to the molecular-genetic classification [16] providing 4 main subtypes of BC. Each of them has its own epidemiology, clinical course, prognosis and approaches to treatment. Thus, in luminal subtype A main target is hormonal therapy, in cases of HER-2 neu overexpression - anti-HER-2 therapy (trastuzumab, lapatinib, pertuzumab, etc.). Recent achievements in BC therapy are associated, most likely, with effective implementation of target therapy strategies. However, this does not apply to basal cell BC, the treatment of which remains one of the biggest problems of current oncology. Basal cell and "triple negative" BC is not always synonymous, although they are often used interchangeably. Approximately 70-75% of basal cell BC have triple-negative phenotype [1,5,6,10] . Approximately in 25% of cases, "triple negative" cancer is not basal cell (in the same group are the so-called rare histologic subtypes BC); 15-20% of basal cell tumors, in turn, are not triple negative [5,10]. In the scientific literature , the immunohistochemical term - "triple negative" is more commonly used due to easier interpretation of the results of clinical trials, as immunohistochemistry is much more affordable than genetic study and used almost routinely. Clinical and epidemiological characteristics of the "triple negative" breast cancer (TNBC) are sufficiently studied and widely known. According to different authors [1,5,6] its frequency ranges from 10 to 20%, it is more common in younger patients, the risk factors are opposite to luminal subtypes [5,6]. In most cases, TNBC histologically represented like low-grade ductal carcinoma. The distinguishing feature of this type of tumor is a high proliferative activity and high rate of growth [1,5,6,10] . TNBC is characterized by an aggressive course, the early appearance of visceral metastases, and as a result, poor prognosis. Thus, according to Dent R., [6] median time from detection of progression to death is in TNBC 9 months versus 22 months in luminal types. According to the results of a retrospective study conducted by Kennecke H. [10] (of archival data of 3726 patients treated between 1986 and 1992), the median

survival for metastatic TNBC was only 6 months, the luminal A subtype - 2.2 years, luminal B - 1.6 years.

One of the paradoxes TNBC is a combination of the worst survival rates with high sensitivity to cytotoxic therapy, especially well demonstrated in neoadjuvant chemotherapy. In this respect one of the most cited studies is theone of Liedtke K., 2008 [14]. This is a retrospective study involving 1,118 patients treated from 1985 to 2004. From them - 255 (23%) – had TNBC. In patients with triple negative BC was detected the highest rate of sensitivity to chemotherapy (pathological complete response rate 22% versus 11% for the other types, P = 0.034). In TNBC the 3-year disease-free survival rate was 63% compared with 76% for other tumors, and 3-year overall survival was 74% versus 89%.

Figure 1 presents data on the survival of patients, depending on the tumor response to neoadjuvant chemotherapy . TNBC patients with complete pathologic response of the tumor had a 3-year overall survival rate 94%, while patients with residual tumor - only 68%. In the other subtypes of BC 3-year overall survival in patients with pathological complete regression was 98%. The result of this study led to the most important conclusion: only patients with a complete pathologic response had a 3-year overall survival rate comparable to that of other types (94% vs. 98%, p = 0.24). It follows that the main purpose of neoadjuvant chemotherapy in TNBC is to achieve pathological complete regression, and no other result can be considered acceptable [14].

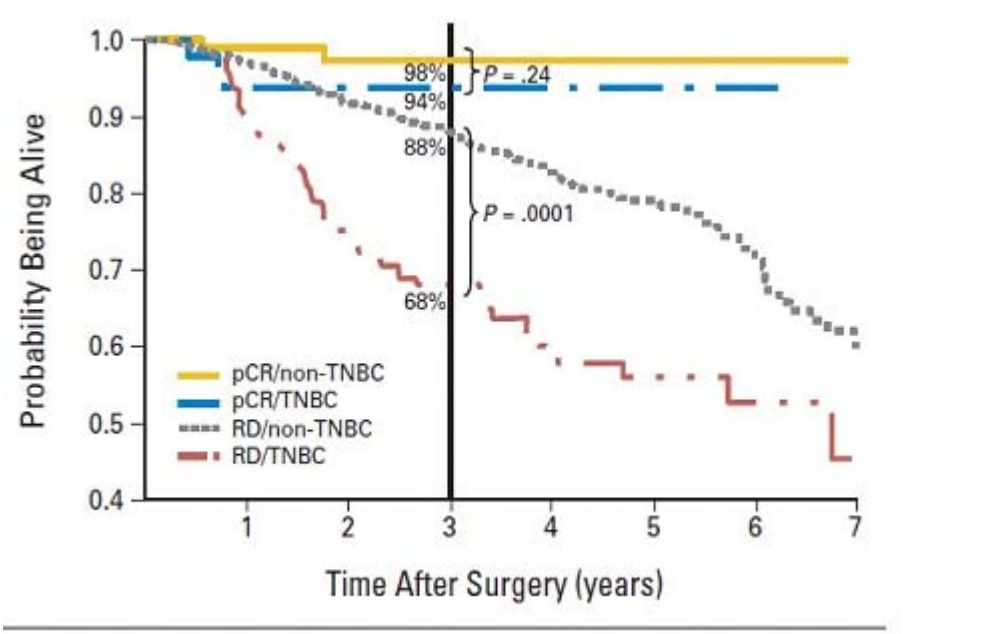

Fig. 1. Overall survival as a function of morphologic response to neoadjuvant chemotherapy

The question of optimal regimen of neoadjuvant chemotherapy of TNBC remains unanswered, although in routine practice the combination of anthracyclines and taxanes is commonly used. Illustrative is the study GEPARTRIO [12], in which the authors used a combination of TAC (docetaxel, doxorubicin, cyclophosphamide). The study included 2072 patients, of whom 509 with TNBC (Fig. 2). The patients with this subtype had the pathological complete regression rate 39% (this is the highest result for neoadjuvant therapy obtained in a prospective randomized study with a large number of patients).

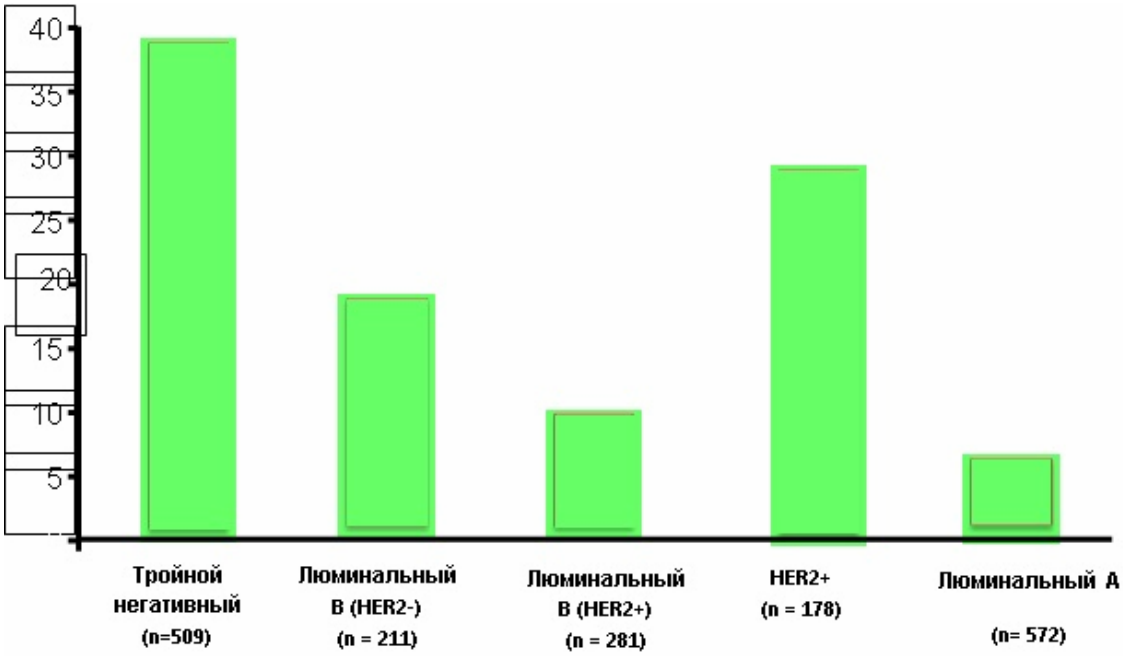

Fig. 2. Complete pathologic response (%) in different breast cancer types. Triple negative, luminal A, luminal B.

Special attention in recent years has attracted the use of platinum in TNBC. The mechanism of action of platinum is in destruction of DNA synthesis by forming interchain cross-links . In recent years it has been shown that platinum agents in TNBC were much more effective in "hereditary» BRCA-associated cancers. Although the rate of BRCA1 / 2- associated BC in general population is around 5%, the vast majority of them are basal cell [10]. In a retrospective study of Byrski T. (2009) the effect of neoadjuvant chemotherapy was analyzed in 102 patients with BRCA-associated BC. The complete pathologic response was achieved only in 8% of patients receiving chemotherapy regimen AT (docetaxel, doxorubicin), in 22% of patients on the regimen FAC (fluorouracil, cyclophosphamide, doxorubicin) and 83% with cisplatin monotherapy [3]. At the same time, however, it should be noted a small number of observations (cisplatin group - 12 patients) and the retrospective nature of this study.

In the regard of an adjuvant chemotherapy of BC is not possible not to mention the results of two meta-analyzes conducted by EBCTCG . The first, published in 2005, included 194 randomized studies conducted in the 80-90s. The main results of this meta-analysis are presented in table 1. Evaluating them it is possible to notice the apparent superiority of adjuvant chemotherapy in patients younger than 50 years, ie in premenopausal women: an increase in 15-year overall and disease-free survival rate on 7-8% (given the huge number of patients the differences have the very high level of statistical significance) [7]. The second meta-analysis (table 2), published in 2008, included only a estrogen negative patients (46 randomized trials). In this category of patients the differences in the 10-year overall and disease-free survival between the age groups are minimal [8].

Table 1. Impact of adjuvant chemotherapy on 15-year overall and disease-free survival. Meta-analysis of 194 randomized studies.

Age younger 50	Age older 50
Increase of disease free survival on 12,3 % *(2p < 0,00001)*	*Increase of disease free survival on 4,1 %* *(2p < 0,00001)*
Increase of overall survival on 10 % *(2p < 0,00001)*	*Increase of overall survival on 3 %* *(2p < 0,00001)*

Table 2. Adjuvant chemotherapy in estrogen negative patients, impact on 10-year survival. Meta-analysis of 46 randomized studies, performed by EBCTCG.

Age younger 50	Age older 50
Increase of disease free survival on 12 % *(2p < 0,00001)*	*Increase of disease free survival on 10 %* *(2p < 0,00001)*
Increase of overall survival on 8 % *(2p < 0,00001)*	*Increase of overall survival on 6 %* *(2p < 0,00001)*

In the large study BCIRG 001 in the adjuvant setting regimen has been compared with FAC [11]. Of the included 192 patients 1491 had a "triple negative" phenotype. In the TNBC group the biggest difference in the 3-year disease-free survival in favor of the TAC regimen was detected: 14% (74% vs. 60%).

In the CALGB 9344 study, patients with the presence of lymph node metastases were administered 4 cycles of FC regimen, after which patients were randomized to the further single-agent paclitaxel 4 cycles or observation (Fig. 3). Addition of paclitaxel resulted in the statistically significant increase in disease-free survival in "triple negative" and HER-2 positive BC patients [13].

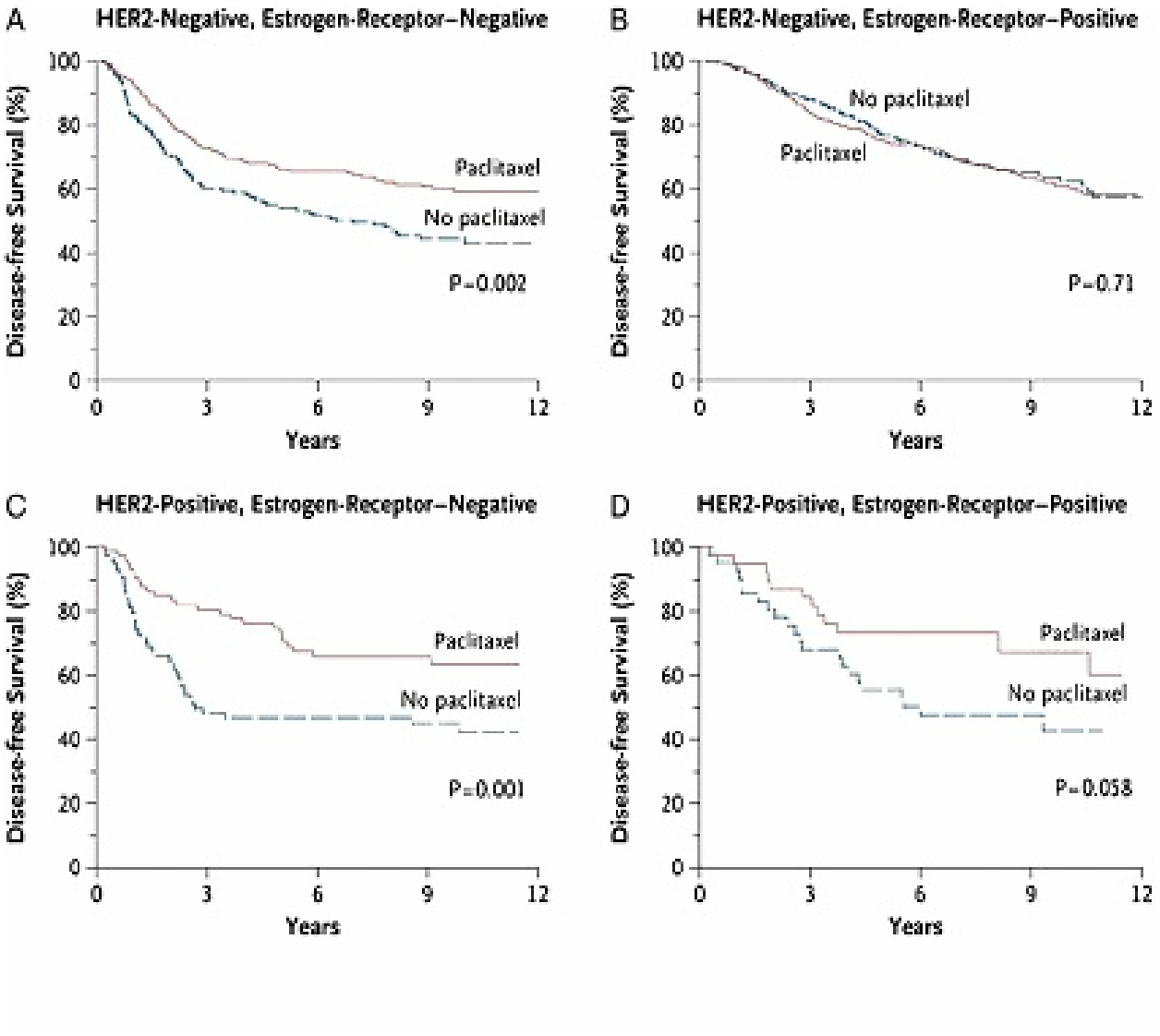

Fig. 3. Disease-free survival among patients treated with or without paclitaxel according to estrogen-receptor status and HER2 expression, CALGB 9344 study

Considering the high proliferative potential of TNBC the use of dose-dense chemotherapy regimens (with reduced intervals between courses) looks promising. In 2010, there was published a meta-analysis of 10 such retrospective studies in the adjuvant setting. There was a moderate increase in disease-free and overall survival with dose-dense mode. However, the authors noted that these data need confirmation in prospective studies [2].

In recent years, there is evidence of possible efficacy of angiogenesis inhibitors in the treatment of metastatic TNBC, bevacizumab in particular. In 2007 was launched BEATRICE study, in which patients with TNBC in adjuvant setting in

addition to anthracycline and / or taxane-containing regimens of chemotherapy received bevacizumab for a year or observation. Preliminary results published in December 2012 did not show statistically significant differences in the 3-year disease-free survival in both groups (83.7% and 82,7%) [2].

Thus, the strategy of maximal individualization of BC therapy in "triple negative" subtype to date has not led to the approval of any specific recommendations. From a practical point of view, the only effective approach is the cytotoxic therapy. Studies in recent years were dedicated to the search and study in TNBC the new "targets", such as EGFR, c-kit, BRCA and other signaling pathways, and the appropriate inhibitors [1,10,13]. Although none of these strategies has not yet had practical results, many ongoing randomized trials can give hope for their appearance in the near future.

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