ACTA MEDICA LITUANICA. 2013. Vol. 20. No. 4. P. 191–198

Triple negative breast cancer: 5-year results of combined treatment

Valerijus Ostapenko[1],

Teresė Pipirienė Želvienė[1],

Giedrė Smailytė[1],

Andrej Ostapenko[1],

Raimundas Meškauskas[2]

[1] *Institute of Oncology, Vilnius University*

[2] *National Centre of Pathology, Vilnius, Lithuania*

Background. Breast cancer is the most common female cancer worldwide. It is a heterogeneous disease with regard to biological behaviour, responses to treatment and prognosis. The term "triple negative breast cancer" (TNBC), namely, refers to the immunohistochemical classification of breast tumours lacking ER, PgR, and HER2 protein expression. TNBC does not respond to endocrine therapy and chemotherapy remains the main systemic therapeutic option in the adjuvant and metastatic setting of TNBC.

The aim of this study was a retrospective analysis of the results of combined treatment for TNBC.

Patient and methods. In our retrospective analysis, we analized 431 patients with TNBC treated with combination therapy from March 2005 until December 2009 at the Institute of Oncology, Vilnius University. 52.20% of the whole group of patients were women older than 50 years. Stage I was diagnosed in 23.9%, stage II in 49.65%, stage III in 22.74%, stage IV in 3.71% of cases. According to pathological types of the tumour ductal invasive carcinoma was diagnosed in 376 patients (87.24%) and tumour grade G3 was determined in 330 patients (76.57%). All 431 patients underwent surgical treatment, 239 patients had chemotherapy (55.45%). The disease-free survival and overall survival were estimated by the Kaplan-Meier method. The Log-rank test was used for survival comparison between the groups. $P < 0.05$ indicated a significant statistical difference. All statistical analyses were performed using Stata Statistical Software Version 11.0.

Results. Five-year overall survival for the whole group of patients was 60.0% (95% CI 54.56–64.96); 5-year overall survival for stage I was 81.92% (95% CI 71.38–88.88); 5-year overall survival for stage II was 66.35% (95% CI 58.46–73.09); 5-year overall survival for stage III was 33.99% (95% CI 23.93–44.29), $p < 0.00001$; five-year disease free survival for the whole group of patients was 56.1% (95% CI 50.18–61.6).

Conclusions. Five-year survival was significantly higher in earlier stages of the disease (81.9%, 66.5%, 34.0% for stages I, II and III), $p < 0.00001$. Different results for the TNBC patient survival can be explained by biologically distinct subtypes of TNBC.

Key words: triple negative breast cancer, 5-year overall survival, 5-year disease free survival

Correspondence to: Valerijus Ostapenko, Institute of Oncology,Vilnius University, Santariškių 1, LT-08660 Vilnius, Lithuania. E-mail: v.ostapenko@takas.lt; valerijus.ostapenko@vuoi.lt

INTRODUCTION

Breast cancer is the most common female cancer worldwide. It is a heterogeneous disease with regard to biological behaviour, responses to treatment and prognosis (1, 2). In 2000, Perou et al. have demonstrated that the expression of ER and HER2 represents two major determinants of breast cancer molecular subgroups (1). Using unsupervised hierarchical clustering, Sorlie et al. pioneered the establishment of a breast cancer classification system distinguishing five distinct breast cancer molecular subgroups (Luminal A, Luminal B, HER2-enriched, basal-like and a normal breast-like group) that show significant differences in incidence, survival and response to therapy. The name "luminal" derives from similarity in expression between these tumors and the luminal epithelium of the breast; they tipically express luminal cytokeratins 8 and 18. The luminal subtypes are characterized by the expression of ER, PR, and other genes associated with ER activation (2). The HER2-enriched subtype (previously the HER2+/ER-subtype) is characterized by high expression of the HER2 and proliferation gene clusters and low expression of the luminal cluster. These tumors are typically negative for ER and PR, and positive for HER2. The basal-like subtype (BLBC), so called because of some similarity in expression of the basal epithelial cells, makes up about 15–20% of breast cancers. The BLBC subtype is more commonly negative (triple negative) for all three (ER, PR and HER2) markers as well as the increased expression of basal cytokeratins such as CK 5/6 and CK17. The terms "triple-negative breast cancer (TNBC)" and "basal-like" are not completely synonymous. The term "TNBC", namely, refers to the immunohistochemical classification of breast tumours lacking ER, PgR, and HER2 protein expression, whereas the BLBC subtype is defined via the gene expression microarray analysis (3, 4). However, the TNBC phenotype currently serves as a reliable surrogate in the clinical practice. In the absence of a specific therapeutic target, conventional chemotherapy is the mainstay of TNBC treatment according to the majority of national and international guidelines (5, 6).

BACKGROUND

The aim of this study was a retrospective analysis of the results of combined treatment of TNBC.

MATERIALS AND METHODS

Patients

In our retrospective analysis, we analized 431 patients with TNBC treated with combined treatment from March 2004 until December 2009 at the Institute of Oncology, Vilnius University. Patients with TNBC were identified from the database of the National Pathology Center.

Treatment decisions regarding the primary surgery and the adjuvant systemic therapy were based on standards of breast cancer treatment during tumour board. All patients had received primary surgery, surgical assessment of the axillary lymph nodes and adjuvant chemotherapy mostly containing anthracyclines (77.99%), according to current national guidelines. All tumours were characterized as estrogen receptor (ER) negative, progesterone receptor (PR) negative, and HER2 negative according to current national guidelines.

The following demografic, clinical and pathological data such as patient age, stage, laterality, menopausal status, pathological tumour size, tumour type, tumour grade, nodal status, hormonal receptor, HER-2 status were determined for all 441 cases. Cases with stage IV were revised and only 16 patients with metastases to the supraclavicular lymph nodes (in the fifth edition AJCC TNM metastases to the supraclavicular lymph nodes were classified as M1 and stage IV, in the sixth and seventh edition as N3 and stage III) were analyzed and evaluated as a separate group. After the completion of the combined treatment, patients were followed-up every three months for two years, every 6 months for the next two years and yearly thereafter.

52.20% of the whole group of patients (225 cases) were women older than 50 years. In this group of patients 93 (41.33%) women were older than 70 years and 27 (29.03%) of them were older than 80 years. 47.80% of the whole group of patients (206 cases) were younger than 50 years. Stage I was diagnosed in 23.9%, stage II in 49.65%, stage III in 22.74%, stage IV in 3.71% of cases. The tumour size was larger than 2 cm in 284 cases (63.57%).

In this group of patients T2 was documented in 69.72%, and T3 in 11.62%. The axillary lymph node was positive (N+) in 48.49% of patients (209 cases); N1 was confirmed in 55.02%, N2 in 32.54%, N3 in 12.44% of patients. Tumour grade G3 was determined in 330 patients (76.57%), tumour grade G2 in 76 patients (17.63%), tumour grade G1 in 11 patients (2.55%). According to pathological types of the tumour ductal invasive carcinoma was diagnosed in 376 patients (87.24%), lobular invasive carcinoma in 18 (4.18%), metaplastic in 14 (3.25%), medullary in 12 (2.78%), apocrine in 8 cases (1.86%). All 431 patients underwent surgical treatment, 239 patients underwent chemotherapy (55.45%). Antracyclines were used in 184 cases (77.99%), CMF in 39 cases (16.31%), taxanes in 16 cases (6.69%). 38 patients (17.63%) of the whole group of 431 underwent irradiation.

Demographic and clinical characteristics as well as treatment options of the study group are presented in Table 1. The average age of the patients was 57.2 ± 13.4 years (median 56, range 25–88 years). At the end of the follow-up 161 patients were dead.

Table 1. Demographic and clinical characteristics and treatment options of the study group (n = 431 patients)

Variable	No. of patients	% of total
Age		
<50	206	47.80
>=50	225	52.20
Stage		
I	103	23.90
II	214	49.65
III	98	22.74
IV	16	3.71
TNM		
T1N0M0	103	23.90
T1N1M0	53	12.30
T2N0M0	106	24.59
T2N1M0	92	21.35
T3N0M0	9	2.09
T3N1M0	23	5.34
T4N0M0	4	0.93
T4N1M0	26	6.03
AnyTAnyN M1	15	3.48
T		
T1	157	36.43
T2	198	45.94
T3	33	7.66
T4	43	9.98
N		
N0	222	51.51
N1	115	26.68
N2	68	15.78
N3	26	6.03
M		
M0	416	96.52
M1	15	3.48
Tumour grade		
G1	11	2.55
G2	76	17.63
G3	330	76.57
Unknown	14	3.25
Tumour histology		
Ductal	376	87.24
Lobular	18	4.18
Metaplastic	14	3.25
Medullary	12	2.78
Sarcoma	1	0.23
Apocrine	8	1.86
Phylloid tumour	1	0.23
Papillary	1	0.23
Total	431	100

Statistical methods

The vital status of the study group was assessed as of September 30, 2012, by passive follow-up, using data from the population registry. The disease-free survival (DFS) and overall survival (OS) were estimated by the Kaplan-Meier method. DFS was calculated from the date of the start of primary therapy to the date of breast cancer recurrence, the date of death from any cause, or the date of the last follow-up. OS was calculated from the date of the start of primary therapy and death of any cause. The Log-rank test was used for survival comparison between the groups. $P < 0.05$ indicated a significant statistical difference. All statistical analyses were performed using Stata Statistical Software version 11.0 (StataCorp. 2009. Stata Statistical Software: Release 11.0 College Station, TX, USA).

RESULTS

The one-year overall survival for the entire study group was 91.2% (95% CI 88.09–93.51), the five-year survival was 60.0% (95% CI 54.56–64.96).

The one-year disease free survival for the entire study group was 83.69% (95% CI 79.71–86.96),

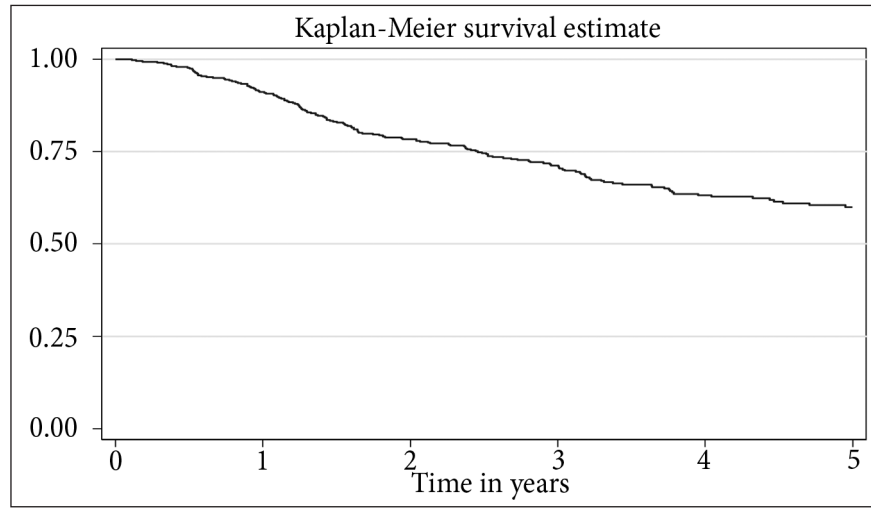

Fig. 1. Five-year overall survival

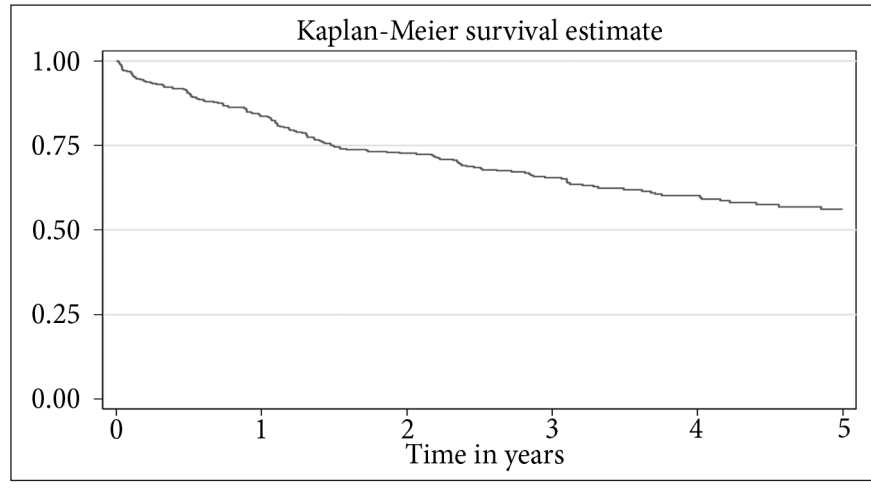

Fig. 2. Five-year disease free survival

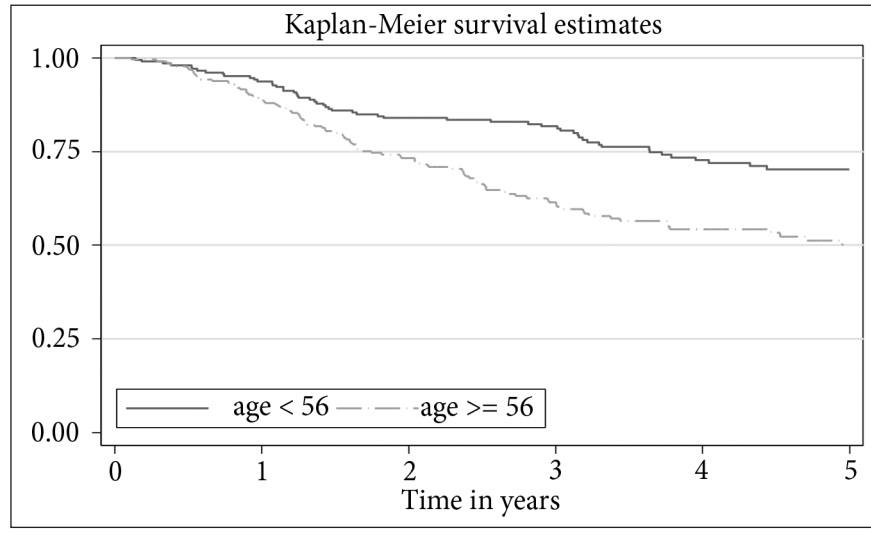

Fig. 3. Five-year overall survival for <56 years and for >=56 years

the five-year disease free survival was 56.1% (95% CI 50.18–61.6).

The five-year overall survival for <56 years was 70.25% (95% CI 62.76–76.52). The 5-year overall survival for >=56 years was 49.965% (95% CI 42.07–57.35); $p < 0.00001$.

The 5-year overall survival for stage I was 81.92% (95% CI 71.38–88.88). The 5-year overall survival for stage II was 66.35% (95% CI 58.46–73.09), the 5-year overall survival for stage III was 33.99% (95% CI 23.93–44.29); $p < 0.00001$.

Table 2. Overall survival, disease free survival and multivariate analysis of prognostic factors of the study group (n = 431 patients)

Variable	1-year	95% CI		5-year	95% CI		Log rank, p
Overall survival	91.18	88.09	93.51	59.98	54.56	64.96	
Disease free survival	83.69	79.71	86.96	56.1	50.18	61.6	
Age							
<56	93.69	89.38	96.29	70.25	62.76	76.52	0.00001
>=56	88.89	84	92.35	49.96	42.07	57.35	
Stage							
I	98.06	92.46	99.51	81.92	71.38	88.88	0.00001
II	95.79	92.07	97.79	66.35	58.46	73.09	
III	80.61	71.31	87.17	33.99	23.93	44.29	
IV	50	24.52	71.05	–	–	–	
Tumour grade							
G1	90.91	50.81	98.67	65.45	23.62	88.3	0.6896
G2	92.11	83.27	96.37	59.64	46.83	70.31	
G3	90.61	86.91	93.3	59.35	53.03	65.11	
Unknown	100	–	–	68.18	34.99	86.96	
Tumour histology							
Ductal	90.69	87.28	93.23	59.29	53.41	64.68	0.5967
Lobular	100	–	–	58.44	31.76	77.76	
Metaplastic	92.86	59.08	98.96	53.04	23.33	75.86	
Medullary	100	–	–	81.48	43.51	95.09	
Sarcoma	100	–	–	100	–	–	
Apocrine	75	31.48	93.09	56.25	14.68	84.15	
Phylloid tumour	100	–	–	100	–	–	
Papillary	100	–	–	100	–	–	

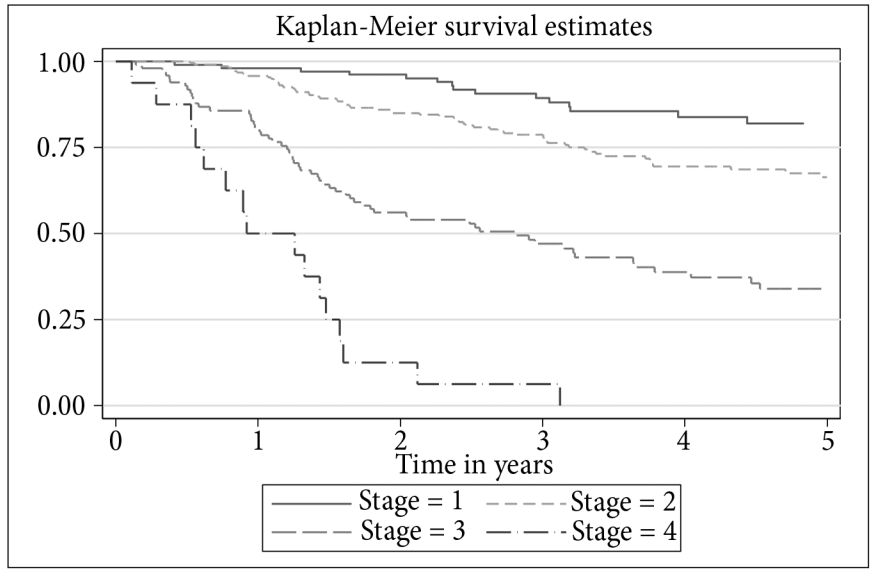

Fig. 4. Five-year overall survival by stage

In our univariate analysis age, stage, and tumour grade were the main prognostic factors. In the multivariate analysis, only age and stage were found to be independent prognostic factors for overall survival.

DISCUSSION

The clinical data of the triple-negative phenotype indicate an aggressive course of this disease and poor clinical outcome of TNBC. The prognostic

value of specific morphological and biological features of these tumours and the results of treatment continue to raise a substantial degree of uncertainty and controversy. The clinical TNBC studies have been limited mostly by small sample sizes and short follow-up times.

The majority of our TNBC patients had relatively large tumours at presentation (T > 2 cm in 63.57% of patients), the dominant type of the tumour was invasive ductal carcinoma (87.24%), the majority of tumours were poorly differentiated (76.57%), almost half of patients had positive axillary lymph nodes at presentation (Table 1).

Simillar data were presented in some previous reports where TNBC were described as relatively large tumours (>2 cm), grade 3 and with a high rate of node positivity (7–9). In the population based Carolina Breast Cancer Study (CBCS), all basal like breast cancers (defined by triple negative status plus EGFR or cytokeratin 5 positivity) were virtually of ductal or mixed histology (90%), and of high grade (84%), which is similar to our results (10). The current theory points out to the suggestion that TNBCs metastasize to axillary nodes and bones less frequently than the non-triple-negative subset of breast tumours, favouring a haematogenous spread. We found that 48.49% of TNBC developed metastasis to lymph nodes. In 34.2% of patientts with T1 TNBC, 46.5% of patientts with T2 TNBC and 71.9% of patientts with T3 TNBC invasion to axillary lymph nodes was confirmed. According to Albergaria et al. (2011) high percentage of axillary lymph node invasion shows that the lymph node involvement in TNBC is as frequent as in other subtypes of breast cancer. The results from published literature showed that TNBC frequently occurred in younger women (<50 years) (12). Advanced age at the time of breast cancer diagnosis has been associated with a slightly increased probability of favourable tumour biology, with node-negative, hormone receptor (HR)-positive, and human epidermal growth factor-2 (HER2)-negative breast cancers being found somewhat more frequently in older women. Nevertheless, a substantial proportion of older women still develop TNBC. A recent review from the United States estimated that ~15% of breast cancers in older patients were TNBC, and in a study from the Shanghai Cancer Hospital, TNBC represented 18.4% of all breast cancers in patients aged ≥70 years (14, 15). Our data showed that 21.58% of the whole TNBC group were patients older than 70 years.

In terms of survival, a sharp decrease has been described in survival during the first 3 to 5 years after diagnosis, but distant relapse after this time is much less common (16, 17). Our data had confirmed a rapid decrease in overall survival during the first 3 years and also had shown a rapid decrease in disease free survival curves during the first 3 years after diagnosis (Figs. 1, 2).

Our results concerning the TNBC overall (60.0% 95% CI 54.56–64.96) and five-year disease free survival 56.1% (95% CI 50.18–61.6) are largely in accordance with published studies. Ortiz (2013) presented the 5-year overall survival of TNBC 47.7% (95% CI 32.2–61.6%) (18). A retrospective study published by Ovcaricek (2010) included 269 TNBC, 53.9% of them were node-negative, the 5-year disease-free survival for the entire group was 68.2% and the 5-year overall survival (OS) was 74.5% (16, 17). In JCO (2013) Metzger-Filho published the results from International Breast Cancer Study Group Trials VIII and IX. In all, 1,951 patients with node-negative, early-stage breast cancer BC subtypes were defined. TNBC was defined in 310 cases and the 10-year overall survival was 75% (19). Our data also confirmed a 5-year overall survival of 82% for TNBC stage I breast cancer.

We found significantly higher survival for younger patients (70.3% vs. 50.0% in age groups <56 and >=56, respectively, $p < 0.0001$). The explanation for this finding was probably the difference in the treatment modalities. 225 patients of the whole group were women older than 50 years, of them 93 were older than 70 years. Due to this fact, mastectomy was the main modality of local treatment; adjuvant chemotherapy was performed in a significantly smaller proportion, mainly by CMF schedule compared with antacyclines and taxanes to younger patients.

According to published data, different results of TNBC patient survival can be explained by biologically distinct subtypes. These subtypes show different histopathological features and a different behaviour that is also reflected by patient survival (20).

CONCLUSIONS

The five-year overall survival for the whole group was 60.0% (95% CI 54.56–64.96).

The five-year survival was significantly higher in earlier stages of disease (81.9%, 66.5%, 34.0% for stages I, II and III), $p < 0.00001$.

Different results of the TNBC patient survival can be explained by biologically distinct subtypes of TNBC.

In patients older than 56 years the 5-year overall survival was 49.965% and for patients younger than >56 years it was 70.3%, $p < 0.00001$.

In our univariate analysis age, stage, and tumour grade were the main prognostic factors. In the multivariate analysis only age and stage were found to be independent prognostic factors for overall survival.

Received 20 September 2013
Accepted 16 January 2014

References

1. Perou CM, Sorlie T, Eisen MB, Rijn M, Jeffrey S, Rees Ch, et al. Molecular portraits of human breast tumours. Nature. 2000; 406: 747.
2. Sorlie T, Perou CM, Tibshirani R, Aras T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001; 98: 10869–74.
3. Parker J, Mullins M, Cheang M, Leung S, Voduc D, Vickery T, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol. 2009; 27: 1160–7.
4. Perou CM. Molecular Stratification of Triple-Negative Breast Cancers. The Oncologist. 2010; 15(Suppl 5): 39–48.
5. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res. 2007; 13: 2329–34.
6. Dawson SJ, Provenzano E, Caldas C. Triple negative breast cancers: Clinical and prognostic implications. Eur J Cancer. 2009; 45: 27–40.
7. Anders KC, Carey LA. Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer. Clin Breast Cancer. 2009; 9 Suppl 2: S73–81.
8. Cleator S, Heller W, Coombes RC. Triple-negative breast cancer: therapeutic options. Lancet Oncol. 2007; 8: 235–44.
9. Nishimura R, Arima N. Is triple negative a prognostic factor in breast cancer? Breast Cancer. 2008; 15: 303–8.
10. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006; 295: 2492–502.
11. Albergaria A, Ricardo S, Milanezi F, Carneiro V, Amendoeira I, Vieira D, et al. Nottingham Prognostic Index in Triple-Negative Breast Cancer: a reliable prognostic tool? BMC Cancer. 2011; 11: 299.
12. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007; 13: 4429–34.
13. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012; 13: e148–60.
14. Yu KD, Li JJ, Di GH, Wu J, Shen ZZ, Shao ZM. A straightforward but not piecewise relationship between age and lymph node status in Chinese breast cancer patients. PLoS One. 2010; 5: e11035.
15. Aapro M, Wildiers H. Triple-negative breast cancer in the older population. Ann Oncol. 2012; 23 Suppl 6: vi52–5.
16. Ovcaricek T, Frkovic SG, Matos E, Mozina B, Borstnar S. Triple negative breast cancer – prognostic factors and survival. Radiol Oncol. 2011; 45(1): 46–52.
17. Gluz O, Liedtke C, Gottschalk N, Pusztai L, Nitz U, Harbeck N. Triple-negative breast cancer – current status and future directions. Ann Oncol. 2009; 20(12): 1913–27.
18. Ortiz AP, Frias O, Perez J, Cabanillas F, Martinez L, Sanchez C, et al. Breast cancer molecular subtypes and survival in a hospital-based sample in Puerto Rico. Cancer Med. 2013 June; 2(3): 343–50.
19. Metzger-Filho O, Sun Z, Viale G, Price KN, Crivellari D, Snyder RD, et al. Patterns of recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: Results from International Breast Cancer Study Group Trials VIII and IX. J Clin Oncol. 2013; 31(25): 3083–90.
20. Aapro M, Wildiers H. Triple-negative breast cancer in the older population. Ann of Oncol. 2012; 23 Suppl 6: vi52–5.

Valerijus Ostapenko, Teresė Pipirienė Želvienė, Giedrė Smailytė, Andrejus Ostapenko, Raimundas Meškauskas

TRIGUBAI NEIGIAMAS KRŪTIES VĖŽYS: PENKERIŲ METŲ KOMBINUOTO GYDYMO REZULTATAI

Santrauka

Įvadas. Krūties vėžys – dažniausia moterų onkologinė liga, heterogeninis susirgimas pagal savo biologiją, atsaką į gydymą ir prognozę. Apie 20 % krūties vėžio atvejų nustatomas trigubai neigiamas krūties vėžys (TNKV). TNKV atspindi imunohistocheminę klasifikaciją, kai navikas neturi nei HER2, nei estrogenų, nei progestinų proteinų ekspresijos. Todėl, esant tiek ankstyvam, tiek išplitusiam TNKV, chemoterapija yra laikoma pagrindiniu TNKV sisteminiu gydymu.

Medžiaga ir metodai. Šiame darbe atlikta retrospektyvinė 431 pacientės, sergančios TNKV ir kombinuotai gydytos Vilniaus universiteto Onkologijos institute nuo 2005 m. kovo mėn. iki 2009 m. gruodžio mėn., analizė. 52,20 % visos tiriamosios grupės sudarė pacientės, vyresnės nei 50 metų. I krūties vėžio stadija diagnozuota 23,9 % tiriamosios grupės ligonių, II stadija – 49, 65 %, III stadija – 22,74 % ir IV stadija – 3,71 %. Patologinio tyrimo duomenimis, duktalinė invazinė karcinoma diagnozuota 376 pacientėms (87,24 % visos grupės), blogai diferencijuota G3 krūties karcinoma – 330 pacienčių (76,57%). 431 pacientei taikytas chirurginis gydymas, chemoterapija – 239 pacientėms (55,45 %). Bendras išgyvenimas ir gyvenimas be ligos apskaičiuoti Kaplan-Meier metodu. Statistinė analizė atlikta panaudojant Stata Statistical Software 11.0 versiją.

Rezultatai. Penkerių metų bendras išgyvenimas visos TNKV tiriamosios grupės sudarė 60,0 % (95 % CI 54,56–64,96); sergančiųjų I stadijos krūties vėžiu penkerių metų bendras išgyvenimas sudarė 81,92 % (95 % CI 71,38–88,88), sergančiųjų II stadijos – 66,35 % (95 % CI 58,46–73,09), sergančiųjų III stadijos – 33,99 % (95 % CI 23,93–44,29), $p < 0,00001$. Penkerių metų bendras išgyvenimas be ligos sudarė 56,1 % (95 % CI 50,18–61,6) visos TNKV tiriamosios grupės.

Išvados. Penkerių metų bendras išgyvenimas statistiškai patikimai aukštesnis esant ankstyvoms ligos stadijoms (81,9 %, 66,5 %, 34,0 % – atitinkamai I, II ir III stadijos); $p < 0,00001$. Skirtingi bendro išgyvenimo rezultatai gali būti paaiškinami biologiškai skirtingais TNKV potipiais.

Raktažodžiai: trigubai neigiamas krūties vėžys, penkerių metų bendras išgyvenimas, penkerių metų bendras išgyvenimas be ligos