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Hypertension prevalence in early breast cancer patients undergoing primary surgery

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ABSTRACT

Purpose: Treatment with chemotherapy and targeted drugs may results in elevated risk of cardiac and renal toxicity as well as hypertension. However, data on prevalence of chronic kidney disease and hypertension in subjects with early breast cancer undergoing primary surgery are very limited.

Patients and methods: The study aimed to assess the prevalence of chronic kidney disease and hypertension (evaluated as a preoperative assessment and defined according to ESC/ESH guidelines) in a cohort of 100 consecutive female patients with early breast cancer treated with primary surgery with curative intent.

Results: Patients with breast cancer were 53 ± 14 years of age, with serum creatinine of 0.68 ± 0.14 mg/dl and estimated glomerular filtration rate by chronic kidney disease-epidemiological collaboration formula of 99 ± 18 mL/min/1.72 m^2. Hypertension was present in 37%, but in the elderly patients (over 65 years) the prevalence was 74%. Hypertensive females had worse kidney function as reflected by higher serum creatinine and lower estimated glomerular filtration rate, higher body mass index and fibrinogen, which reflects general inflammatory state. When we divided the patients according to age (≤ vs > 65 years) and the presence of hypertension, the elderly hypertensive females had significantly worse kidney function, higher fibrinogen and fasting glucose.

Conclusions: The prevalence of hypertension in patients with breast cancer raises with age, and presence of comorbidities, including chronic kidney disease. Hypertension should be treated promptly to prevent cardiovascular complications during oncological therapy.

1. Introduction

In the last decades, survival of cancer patients improved significantly, however, toxicities of antitumor drugs, increased number of elderly patients with many comorbidities, accompanied by not sufficient knowledge and risk factors' management, result in a rise in cardiovascular morbidity in patients with malignancy [1]. Cardiovascular disease (CVD) became the second leading cause of long-term morbidity and mortality among cancer survivors [1]. Both chemotherapy and targeted therapies result in a rise in cardiac and renal toxicities as well as hypertension [2]. According to The American Cancer Society, one in three US citizens can expect to be diagnosed with malignancy in their lifetime, for female the lifetime risk is 37.5% and for male 40.8% [3]. These two serious and often chronic conditions overlap significantly. Hypertension is a modifiable risk factor that can be detected early and treated effectively. Due to the coincidence of high prevalence of cardiovascular risk factors with the presence of prior CVD, multidisciplinary approach appears crucial to optimize and standardize the management of this population of patients. However, data on prevalence of hypertension in patients with malignancy undergoing surgery are very scarce. In addition, prevalence of chronic kidney disease (CKD) is high in patients with malignancy [4], but data are also limited. Two studies [5,6] observed a high CKD prevalence of ~33 and 27%, respectively. It is of utmost importance to thoroughly assess each subject, including anamnesis and current medical treatment, to screen for hypertension and CKD to lower the toxicity of the therapy as much as possible, to choose the optimal adjuvant treatment thereafter. Breast cancer is treated with potentially cardio- and vasculotoxic chemotherapies as well as targeted therapies [7].

The aim of the present study was to evaluate the prevalence of

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Table 1
Clinical and biochemical data of patients with and without hypertension.

	Normotensive n = 63	Hypertensive n = 37
Age (years)	48.1 ± 13.4	60.5 ± 10.8*
BMI (kg/m^2)	25.3 ± 5.2	30.2 ± 8.9***
Sodium (mEq/L)	140.6 + 1.9	140.4 + 2.2
Potassium (mEq/L)	4.37 ± 0.41	4.35 ± 0.39
Hematocrit (%)	40.4 ± 3.7	41.0 ± 3.1
Hemoglobin (g/dL)	13.5 ± 1.4	13.7 ± 1.1
Erythrocyte count (×10^{12}/μL)	4.42 ± 0.79	4.5 ± 0.43
MCV (fL)	104.1 ± 10.3	91.3 ± 4.9
RDW (%)	12.2 ± 1.3	11.6 ± 0.7
Leukocyte count (×10^6/μL)	6.00 ± 1.48	6.20 ± 1.72
Platelet count (×10^{12}/μL)	247.1 ± 108.1	241.4 ± 67.0
Creatinine (mg/dL)	0.66 ± 0.12	0.72 ± 0.15*
Urea (mg/dL)	28.5 ± 13.2	32.5 ± 9.6
eGFR by CKD-EPI (mL/min/1.72 m^2)	104.0 ± 15.5	89.3 ± 17.9***
APTT (s)	29.4 ± 5.1	30.2 ± 6.2
INR	1.01 ± 0.07	1.00 ± 0.05
Fibrinogen (mg/dL)	271.8 ± 61.9	306.0 ± 44.5*
Glucose (mg/dL)	107.9 ± 27.4	118.6 ± 31.8

BMI, body mass index; MCV, mean corpuscular volume; RDW, red cell distribution width; eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease-epidemiological collaboration formula; APTT, activated partial thromboplastin time; INR, international normalized ratio.
* $p < 0.05$.
*** $p < 0.001$.

hypertension and CKD in a cohort of patients with breast cancer undergoing primary surgical treatment with curative intent.

2. Patients and methods

The pilot study was performed on the consecutive 100 subjects with breast cancer undergoing primary surgery with curative intent in one year in the Department of Oncological Surgery. No neoadjuvant therapy was administered before the surgery. The local Bioethical Committee gave consent for the study (R-I-002/56/2018). The basal clinical and biochemical characteristics are presented in Table 1. Data analyzed were based on the demographical, clinical and laboratory data enclosed in patients' medical charts. Blood pressure was measured using standard protocols as a part of the preoperative assessment. Hypertension was defined as either a blood pressure of at least 140/90 mm Hg or hypertension medication use according to the current European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines [8]. CKD was defined according to 2012 Kidney Diseases Improving Global Outcomes (KDIGO) guidelines [9] with glomerular filtration rate (GFR) estimated using chronic kidney disease-epidemiological collaboration formula (CKD-EPI) [10].

For data analysis Statistica 13.1 computer software (Tulsa, OK, USA) was used. Normality of variable distribution was tested using Shapiro–Wilk *W*-test. Mann–Whitney rank sum *U* test or Student's *t*-test were used in statistical analysis to compare differences between groups with $p < 0.05$ considered statistically significant, when appropriate.

3. Results

The prevalence of hypertension was 37% among the patients studied. Mean age was 52.7 ± 13.8 years. Table 1 presents the clinical characteristics of the analyzed patient population. Hypertensive females had worse kidney function as reflected by higher serum creatinine and lower eGFR by CKD-EPI formula, higher body mass index (BMI) and fibrinogen, which reflects general inflammatory state. The prevalence of hypertension in patients over 65 years was 74%. When we divided the patients according to age (≤ vs > 65 years) and the presence of hypertension, the elderly hypertensive females had statistically significantly higher serum creatinine (0.75 ± 0.18 mg/dL vs 0.64 ± 0.11 mg/dL, $p < 0.05$) and lower corresponding eGFR by CKD-EPI formula (79.49 ± 25.80 mL/min/1.72 m^2 vs 101.11 ± 12.53 mL/min/1.72 m^2, $p < 0.001$), significantly higher fibrinogen (354.00 ± 30.32 mg/dL vs 265.73 ± 59.34 mg/dL, $p < 0.01$) and fasting glucose (137.00 ± 68.73 mg/dL vs 104.30 ± 14.47 mg/dL, $p < 0.01$). In the studied group the prevalence of CKD was 5% whereas in the elderly patients it was 25%.

Odds ratio (OR) for hypertensives older than 65, obese (BMI > 30 kg/m^2) and with eGFR < 6060 mL/min/1.72 m^2 were as follows 1.33 (95% CI 0.65; 2.72), 0.69 (95% CI 0.30; 1.61) and 0.94 (95% CI 0.49; 1.77), respectively.

4. Discussion

In our study, hypertensive females with breast cancer undergoing primary surgery with curative intent accounted for over one third of patients. We assessed the prevalence of hypertension according to current ESH/ESC [7] guidelines during evaluation before planned primary surgery with curative intent. However, according to the new American Heart Association/American College of Cardiology (AHA/ACC) guidelines, hypertension stage 1 is defined as systolic blood pressure (SBP) between 130–39 mmHg or diastolic blood pressure (DBP) between 80–89 mmHg, hypertension stage 2 is diagnosed with SBP ≥140 mmHg or DBP ≥90 mmHg on two or more properly measured readings during each of two or more ambulatory visits after an initial screening [11]. Ambulatory blood pressure monitoring is generally employed in the randomized control trials in hypertension, however, not in every study, as in the SPRINT [12] who paved the way to the new AHA/ACC guidelines. These 2017 ACC/AHA hypertension guidelines state that the hypertension prevalence in women aged 65–74 years in the USA is 78% [6]. With current European [7] and our national Polish guidelines [13] the hypertension prevalence in women over 65 years of age was comparable to US females when applying the new AHA/ACC guidelines. It reflects the high prevalence of hypertension in the elderly breast cancer patients and may have a significant impact on the outcomes. In the PolSenior study, the prevalence of hypertension in females aged 65 years or older was 78.2% and in the group aged 65–69 years the prevalence of hypertension was 76.6% with isolated systolic hypertension of 12.5% [14].

Our findings are of very important clinical relevance as both doctors and patients usually consider diagnosis of breast cancer of utmost

medical priority and thereby may neglect the CVD risk. It may result in suboptimal diagnosis and therapy of comorbidities such as CVD, particularly in the elderly [15]. Harlan et al. [16] studied the prevalence of comorbidities in patients with breast cancer at the time of diagnosis and 30 months post-diagnosis. The most common comorbidity was hypertension. However, it should be stressed that hypertension was less often reported in the hospital medical charts (28%) than in the NHANES data (34%) ($p < 0.05$). They stressed, that in general, women treated with adjuvant therapy were more prone to have de novo comorbidities and efforts should be exercised to lower the risk of new comorbidities due to chemotherapy and other combination treatment. Women's Health Initiative study [17], prospectively assessed postmenopausal females and it was found that CVD affected mostly females aged 70–79 years of age with localized breast cancer. The authors stressed that CVD was the leading cause of mortality (22%) during 10 years follow-up, whereas only 17% died due to breast cancer. Hypertension was present in 28.5% females without CVD and in 42.4% with CVD from the enrollment to the study [17]. It is of high clinical relevance as in our population 74% of breast cancer patients over 65 years old were hypertensive. Nickel et al. [18] studied a cohort of 11,973 women (age range 18–64 years) undergoing mastectomy, and reported that the revised estimate for hypertension was 24.87% [18]. It was similar to the study by Loh et al. [19], where 46.7% patients manifested comorbidities not related to cancer. The most prevalent was hypertension (24.3%), followed by hyperlipidemia (13.1%) and diabetes (5.6%).

There is no data available on the prevalence and effect of prior CVD risk factors before diagnosis of breast cancer on cardiovascular disease after diagnosis of breast cancer in long-term longitudinal studies among older breast cancer survivors relative to women without this malignancy. Haque et al. [20] reported that post-diagnosis history of cigarette smoking, diabetes mellitus, and hypertension evaluated after the diagnosis of breast cancer were stronger predictors of CVD afterwards when compared to breast cancer status. Therefore, CVD risk factors should be identified timely and controlled appropriately in particular in the elderly females diagnosed with breast cancer. This strategy will likely result in an improvement in the overall survival of elderly females with localized breast cancer. Chronic heart failure – a serious complication of anthracyclines – is associated with a significant reduction in the left ventricle ejection fraction and is predicted by a history of hypertension. In addition, patients who received trastuzumab for HER-positive breast cancer may have an elevated risk of hypertension in a population-based cohort of breast cancer cases who were diagnosed at the age between 50 and 74 years [21]. Chemotherapy is a CVD risk factor, when combined with radiotherapy, leads to rise in the incidence of events by 30% relative to the general population [2]. Hypertension appears to be also a surgical risk in cancer patients [22] thus treating this comorbidity would optimize pre-, peri- and postoperative care. It is of utmost importance as Jovenaux et al. [23] stated in the recent survey on prescription of cardiotoxic therapies by oncologists that almost all oncologists prescribed this type of treatment with anthracyclines being the most common (83%), followed by trastuzumab (51%) and other antiangiogenic drugs (64%) [23]. Only one third of the medical oncologists employed expert oncology society guidelines to cope with cardiotoxic events, whereas none of them used or was aware of recommendations from expert cardiology societies. Moreover, hypertension treatment was inconsistent. It was concluded that medical oncologists are disparate in the field of toxicity of the cardiovascular system. In addition, there are no substantial long-term data or guidelines for a special therapeutic strategy available in cancer patients. Only patients treated with antiangiogenic drugs have recommendations in 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines [24]. In the most recent 2018 ECS/ESH guidelines for the management on the arterial hypertension it was stated that in patients treated with inhibitors of vascular endothelial growth factor signaling pathway and the proteasome inhibitors, patients developing hypertension or showing an increase in diastolic blood pressure ≥ 20 mm Hg compared with the pretreatment values, should initiate or optimize hypotensive therapy. The preferred drugs mentioned were blockers of RAA (renin–angiotensin–aldosteron) system and calcium channels blockers. It was also stated that temporary withdrawal could be considered in case of exceedingly high blood pressure despite multidrug regime, severe hypertension-generated symptoms or when cardiovascular event require effective blood pressure control [8].

Data on the CKD prevalence in the early breast cancer patients are very limited. In the Renal Insufficiency and Anticancer Medications (IRMA) study, in almost all of the 1898 patients with breast cancer out of 4684 patients with solid tumors, the prevalence of CKD was very high despite normal creatinine [25]. It was found that 57.1 and 56.0% of those patients had abnormal renal function (below 90 mL/min) using the Cockcroft-Gault or abbreviated MDRD formulae (aMDRD), respectively. In the Belgian Renal Insufficiency and Anticancer Medications (BIRMA) study [26], in breast, colorectal, lung, prostate, and gynecologic cancers, abnormal kidney function i.e. aMDRD < 90 mL/min/1.73 m^2 was reported in 67.8, 59.5, 52.6, 62.6, and 69.6%, respectively, at the same time in this manuscript shows that CKD (eGFR by MDRD < 60 mL/min/1.73 m^2) was found in slightly less than 20% of the breast cancer patients. In our present study, the prevalence of CKD (by CKD-EPI formula) was only 5%.

Some antineoplastic drugs, especially some bisphosphonates, capecitabine and platinum salts, are potentially nephrotoxic and/or require adjustment of the dosage, thus assessment of kidney function is of utmost importance. It was reported that 80.2% of the patients were treated with at least one drug that requires adjustment of the dosage in renal insufficiency and 10.2% with at least one drug for which no data was available, leading to 90.4% in total [27]. In addition, in the IRMA study, the vast majority of the patients with breast cancer were prescribed nephrotoxic drugs. It was reported that 76.85% of the treated patients received at least one nephrotoxic drug. Other important drugs in breast cancer such as anthracyclines, taxanes or trastuzumab do not require dosage adjustment, and are not potentially nephrotoxic. In our study patients were not treated with neoadjuvant therapy, and adjuvant therapy was administered if indicated after the primary surgery with curative intent. It is of overriding significance to be aware of the kidney function in subjects treated with nephrotoxic or potentially nephrotoxic drugs, and to regularly monitor kidney function, before each cycle of therapy during anticancer treatment. Cancer and Leukemia Group B (CALGB) 49,907 trial assessed the effect of pretreatment renal function and 5 end-points: toxicity, dose adjustment, completion of the therapy, relapse-free survival, and overall survival, in patients over 65 years of age with early-stage breast cancer on standard therapy with either cyclophosphamide/doxorubicin (AC) or cyclophosphamide/methotrexate/fluorouracil (CMF) over single-agent capecitabine. The incidence of CKD (stage 3 or 4) was high and reached 72%, 64%, and 75% for treatment with CMF, AC, and capecitabine, respectively [28]. Baseline renal function, according to Cockcroft-Gault formula, was statistically significantly correlated to the occurrence of non-hematologic toxicity for the AC regimen, very mildly for the treatment with capecitabine, and not correlated for the therapy with CMF regimen [28].

In tertiary cancer center in Brazil, when kidney function was estimated in elderly patients by the MDRD formula, 66% (439/666) had impaired kidney function (< 90 mL/min). In breast cancer patients, 17% had eGFR by MDRD lower than 60 mL/min [29]. In retrospective study on 8223 cancer patients in South Korea with one or more serum creatinine assessment from January 1, 2000 to December 31, 2004, the CKD prevalence in breast cancer patients was 3.6% [30]. These results are similar to our study. Moreover, as shown in this study, the CKD was associated with a rise in the overall death rate of patients with malignancy (including breast cancer) of about 12% [30]. It was independent

of other known risk factors [30]. In the Danish Breast Cancer Co-operative Group including 59,673 females without prior malignancy diagnosed with early-stage breast cancer in Denmark in years 1990–2008 with follow-up period of almost 15 years, 16% of patients had comorbidities at breast cancer diagnosis [31]. More importantly, several comorbidities including renal diseases, increased the risk of all-cause death. It was stressed, that increased risk of death was attributed when comorbidities were diagnosed within 5 years following breast cancer diagnosis when compared to 5 years period before breast cancer diagnosis with comorbidities present at that time.

Recently we reviewed the problem of hypertension in malignancy [32]. The possible underlying mechanisms of hypertension in anthracyclines-treated patients are multifactorial and include oxidative stress together with apoptotic/fibrotic inflammatory changes in vasculature and dysfunction of endothelium [32]. Cyclophosphamide, an alkylating agent, another component of prevalent AC regimen in the therapy of early breast cancer, may cause hypertension due to dysfunction of the endothelium, vasoconstriction of the arteries together with renal and vascular damage [32]. In addition, steroids, used as adjunctive therapy are associated with salt and volume retention resulting in hypertension [32].

5. Conclusions

To yield the best possible outcomes in the management of hypertensive cancer patients, meticulous attention should be paid to: screening for risk factors before introducing any oncological treatment, robust monitoring of the cardiovascular system, and early intervention for preexisting comorbidities. It is also of utmost importance for the hypertensive patients to be treated accordingly to prevent any possible complications.

Additionally, the association between CKD and mortality should be brought to the attention of physicians, in particular nephrologists and oncologists, that it is crucial to assess, monitor and manage kidney function in patients with malignancy to prevent or at least ameliorate kidney impairment and potentially impact the overall survival.

Conflict of interests

The authors declare no conflict of interests.

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Authors contribution

Study design: Jolanta Malyszko, Klaudia Kozlowska, Leszek Kozlowski.

Data collection: Klaudia Kozlowska.

Statistical Analysis: Klaudia Kozlowska.

Data Interpretation: Klaudia Kozlowska, Leszek Kozlowski.

Manuscript Preparation: Jolanta Malyszko, Klaudia Kozlowska.

Literature Search: Jolanta Malyszko, Klaudia Kozlowska, Leszek Kozlowski.

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