The influence of obesity on results of AT (doxorubicin plus docetaxel) neoadjuvant chemotherapy in locally advanced breast cancer patients

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The achieve pathologic complete response is proven to be the most important parameter of prognosis. Thereports evaluating the impact of obesity on the obtained pathologic response to chemotherapy are unequal.

The aim of the study was to evaluate in locally advanced breast cancer patients, treated with AT(doxorubicin plus docetaxel) neoadjuvant chemotherapy: 1. The relationship of obesity with obtaining pathological response. 2. The relationship of obesity and free of disease recurrence survival (DFS) and overall survival (OS) associated with the tumour.

Material and methods. A retrospective study was carried out in a group of 105 patients with locally advanced breast cancer, treated with AT neoadjuvant chemotherapy and then treated with radical surgery. Two variants of pathological response have been adopted: a pCR (T0N0) and pCR1 (TisN0, TxN1, T1N0, T1N1, T0N1). The relationship of obesity with pathological response and survival was investigated.

Results. In univariate analysis the pCR1 was obtained with its arising from the borderline of statistical significance with lower incidence of obesity. In pCR1 multivariate analysis, negative pCR1 relationship with obesity was on the borderline of the statistical significance. The multivariate analysis showed a significant negative association OS with obesity (p=0.047) and positive with the occurrence of menopause (p = 0.029).

Conclusions. In patients with locally advanced breast cancer treated with AT neoadjuvant chemotherapy, the obesity seems to be an independent and unfavourable predictor of the lack of obtaining pCR1 pathological response. 2. In the multivariate analysis, the obesity was a significant independent factor related to shorter OS.

Key words: obesity, neoadjuvant chemotherapy, breast cancer

In the majority of patients with IIIA and IIIB breast cancer according to pTNM classification, the first stage of treatment is preoperative chemotherapy. It was proved that the patients’ survival time does not depend on the sequence of local and systemic treatment, whereas preoperative chemotherapy (CHT) or hormone therapy increases the chances for breast-conserving therapy (1, 2, 3). Pathological complete remission in the tumour (pCR) or pathological complete response in axillary lymph nodes (npCR) are considered to be a predictive factor of overall survival (OS) and disease-free survival (DFS) (4).

In practice obesity is diagnosed using the body mass index (BMI). BMI was assumed to
be normal in the rage 18.5-24.9 kg/m\(^2\), BMI ranging from 25 to 29.9 kg/m\(^2\) indicated overweight, and obesity was diagnosed when BMI was over 30 kg/m\(^2\). Obesity is often accompanied by insulin resistance, secondary hyperinsulinism, secondary ovarian disorders, changes in the diurnal secretion rhythm of growth hormone, cortisol and prolactin, changes in fatty tissue reactivity on catecholamines and thyroid hormones (5). The likely mechanism of relationship between obesity and breast cancer results from interactions between circulating oestrogens originating from peripheral aromatization in fatty tissue, effects of insulin-like growth factor (IGF-1) axis and function of adipocytes as an endocrine organ (6).

In postmenopausal women oestrogens are mainly produced in fat cells by aromatization of androstenedione to oestrone (7). Obese postmenopausal women have a higher level of circulating oestrogens compared to patients with normal body mass and are proved to be at about three times higher risk of breast cancer development (8). Obese breast cancer patients are at greater risk of treatment complications, greater risk of cancer recurrence, show shorter overall survival and more frequent generalization of cancer compared to patients with normal body mass (9).

In the available publications, however, the studies usually included patients at different stages of tumour development and treated with different regimens of induction chemotherapy (1, 4, 10, 11, 12). The present study analyses consecutive cases of patients only with breast cancer stage III, treated with one type of preoperative chemotherapy with doxorubicin and docetaxel, then subjected to radical surgery of the tumour.

Study purpose: 1. To evaluate the relationship of obesity with pathological response to AT (doxorubicin plus docetaxel) neoadjuvant chemotherapy in locally advanced breast cancer patients. 2. To evaluate the relationship of obesity with disease free survival (DFS) and tumour-related overall survival (OS) in patients with locally advanced breast cancer treated with AT neoadjuvant chemotherapy.

**MATERIAL AND METHODS**

The retrospective study was carried out in 105 unselected consecutive patients after radical surgery due to locally advanced breast cancer (stages IIIA, IIIB, IIIC) who received AT neoadjuvant therapy (docetaxel 75 mg/m\(^2\) given as one-hour intravenous infusion on day 1 and doxorubicin 50 mg/m\(^2\) given as 30-minute intravenous infusion on day 1 of the 21-day cycle). The patients were treated in West Pomeranian Oncology Centre in Szczecin from October 2001 to December 2006. Histological or cytological diagnosis of cancer was confirmed before the start of oncological treatment. The presence of distant metastases was excluded at cancer diagnosis. Induction chemotherapy included 4 cycles of chemotherapy according to the AT regimen. The next stage of the treatment was modified radical mastectomy. The patients additionally received 4 cycles of chemotherapy after the surgery. The selection of postoperative chemotherapy regimens was at the discretion of the physician in charge. All patients received supplementary radiotherapy of 50 Gy in 2 Gy fractions to the chest and regional lymph nodes.

Supplementary hormone therapy with tamoxifen was used in hormone-sensitive cancers. In premenopausal patients tamoxifen therapy was accompanied by pharmacological castration with goserelin for 2–3 years. In 9 postmenopausal patients after 2–3 years of tamoxifen treatment, the hormone therapy was switched to non-steroid aromatase inhibitor anastrozole or letrozole. Supplementary hormone therapy was carried out for 5 years. Information on clinical and pathological data, treatment method and fate of patients was obtained from medical records. The follow-up after treatment completion was conducted based on the current standards. 51 subjects (48.6%) had IIIA, and 54 (51.4%) had IIIB+C cancer stage. Basic clinical and pathological data are presented in tab. 1.

Median BMI was 25.95 (min. 18.49, max 47.07). The patients were divided into 3 groups: I – BMI ≤ 25 (41% of patients), II – BMI 25–30 (31.4% of patients), III – BMI ≥ 30 (27.6% of patients). The status of ER and HER2 receptors in the tumour was evaluated in all cases. Expression of progesterone receptors (PR) was evaluated in 49 cases, including all cancers without ER expression (ER-). The presence of ER (ER+) expression was found in 58.1% of subjects. The presence of progesterone receptor (PR+) expression was found in 6 cases, and the
Table 1. Clinical and pathological data on the subjects

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>n=105 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>49.9 (min 25, max 66 years)</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td></td>
</tr>
<tr>
<td>≤ 25</td>
<td>43 (41%)</td>
</tr>
<tr>
<td>25-30</td>
<td>33 (31%)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>29 (28%)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
</tr>
<tr>
<td>premenopausal</td>
<td>50 (47.6%)</td>
</tr>
<tr>
<td>postmenopausal</td>
<td>55 (52.4%)</td>
</tr>
<tr>
<td>Oestrogen receptors</td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>61 (58.1%)</td>
</tr>
<tr>
<td>negative</td>
<td>44 (41.9%)</td>
</tr>
<tr>
<td>Progesterone receptors*</td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>6</td>
</tr>
<tr>
<td>negative</td>
<td>43</td>
</tr>
<tr>
<td>Hormone-dependent</td>
<td>63 (60%)</td>
</tr>
<tr>
<td>Hormone-independent</td>
<td>42 (40%)</td>
</tr>
<tr>
<td>HER2**</td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>29 (30.5%)</td>
</tr>
<tr>
<td>negative</td>
<td>66 (69.5%)</td>
</tr>
</tbody>
</table>

BMI – body mass index
HER2 – human epidermal growth factor receptor 2
* PR expression was evaluated in 49 cancer cases, including all ER(+) cancers
** HER2 expression was assessed in 95 cancers

Absence of PR expression (PR-) was observed in 43 cancers. Patients with present expression of ER(+) and PR(+), as well as ER(+)PR(-), ER(-)PR(+) receptors were included in the hormone-dependent group (n=63, 60% of the subjects). The cancers that did not show ER and PR expression were classified to the hormone-independent group. HER2 status was evaluated in all cases except for 10 patients due to an insufficient amount of material. 29 subjects (30.5%) were classified to the HER2 positive group. Two variants of pathological response to the treatment were adopted: pCR (T0N0 – no neoplastic tissue found in the surgical specimen) and pCR1 (≤ 20 mm tumour found in the surgical specimen, neoplastic involvement of ≤ 3 neighbouring axillary lymph nodes). The group with pCR1 included patients with TisN0, TxN1, T1N0, T1N1, T0N1 found in the surgical specimen and patients from the pCR (T0N0) group. Pathological complete response (pCR) was achieved in 9 patients (8.6%). The pCR1 response was achieved in 41 (39%) patients. Survival analysis was performed for all subjects. The DFS was defined as the time from the beginning of chemotherapy to the relapse of cancer in the form of a local recurrence or remote metastasis. The OS was defined as the time from the start of chemotherapy to cancer-related death or to the last visit to the chemotherapy department at least 5 years from the start of cancer treatment. During the follow-up, cancer recurrence was observed in 29 subjects (27.6%). Death due to cancer occurred in 20 patients (19.1%). Death due to reasons not directly related to cancer occurred in 4 cases. During the follow-up, death occurred in 24 subjects (22.9%), 81 subjects (77.1%) are still living. Mean OS was 84.4 months (min 16 months, max 129.5 months). The study was granted approval No 0012/32/04/2014 by the Bioethics Committee.

Statistical analysis. Associations between nominal features were analysed using the chi-square test and two-sided Fisher’s exact test. Values of measurable variables were compared between the groups using the Mann-Whitney test. A logistic regression model was used for multivariate analysis of the likelihood of achieving response to the treatment. Uni- and multivariate analysis of survival was made using the Cox proportional hazard model. Statistical significance threshold was set at p<0.05, and associations of 0.05<p<0.1 were considered to be at the borderline of statistical significance. Calculations were made with STATISTICA 10 software.
RESULTS

Pathological response

Pathological complete response pCR (pT0-pN0) was achieved in 9 patients (8.6%). Univariate analysis did not show any significant association between achieving pCR and any of the investigated factors. Pathological response of at least pCR1 (pT0pN0 + pT1pN1 + pTxN1 + pT1N0 + pT1N1 + pT0N1) was achieved by 41 subjects. In univariate analysis, the association between the achievement of pCR1 response and slightly lower incidence of obesity was at the borderline of statistical significance (24% vs 45%, p=0.073, fig. 1).

In univariate logistic regression model, obesity was associated with slightly lower rate of pCR1 response to chemotherapy (association at the borderline of statistical significance, p=0.057, OR 0.39, 95% CI: 0.148–1.041). In multivariate analysis of pCR1 (logistic regression model) taking into account age, menopause, cancer stage, T, N, hormone-dependency and obesity, only negative association of pCR1 with obesity, and positive with hormone-dependency were at the borderline of statistical significance (respectively p=0.092, OR 0.407, 95% CI: 0.141–1.175 and p=0.078, OR 2.205, 95% CI: 0.903–5.381. Multivariate analysis of pCR1 (logistic regression model) in the subgroup (n=95) with determined HER2 status taking into account age at diagnosis, hormone-dependency, HER2, T, N, menopause, stage of cancer and obesity, showed only negative association at the borderline of statistical significance between pCR1 achievement and obesity (p=0.082, OR 0.371, 95% CI: 0.119–1.154).

Disease free survival time (DFS) (n=105)

Univariate analysis showed only negative association between DFS and involvement of regional axillary lymph nodes (p=0.013). In multivariate analysis of DFS, only the association between obesity and shorter DFS was at the borderline of statistical significance (p=0.08) (tab. 2).

Overall survival time (OS)

Univariate analysis (n=105) only showed negative association between OS and involvement of regional axillary lymph nodes (p=0.049). Multivariate analysis of OS (n=105) only

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>DFS Hazard ratio (95% CI)</th>
<th>p</th>
<th>OS Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at cancer diagnosis (years)</td>
<td>1.029 (0.976-1.085)</td>
<td>0.29</td>
<td>1.043 (0.978-1.112)</td>
<td>0.20</td>
</tr>
<tr>
<td>Hormone-dependency</td>
<td>1.833 (0.792-4.246)</td>
<td>0.16</td>
<td>1.141 (0.449-2.900)</td>
<td>0.78</td>
</tr>
<tr>
<td>Menopause</td>
<td>0.416 (0.147-1.183)</td>
<td>0.10</td>
<td>0.218 (0.056-0.857)</td>
<td>0.029</td>
</tr>
<tr>
<td>Cancer stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB + IIIC vs IIIA</td>
<td>1.112 (0.522-2.369)</td>
<td>0.78</td>
<td>0.583 (0.226-1.506)</td>
<td>0.265</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.177 (0.909-5.216)</td>
<td>0.08</td>
<td>3.146 (1.015-9.756)</td>
<td>0.047</td>
</tr>
</tbody>
</table>
showed significant association of OS with obesity (higher risk of death, p=0.047) and with menopause (lower risk of death, p=0.029) (tab. 2).

DFS and OS analysis in a group of patients with determined HER2 expression (n=95)

Univariate analysis in this subgroup did not show any association of DFS and OS with HER2 expression (p=0.96 and p=0.76, respectively). Also multivariate analysis of DFS did not show any significant association between the investigated parameters and DFS. On the other hand, in multivariate analysis of OS taking into account age, hormone-dependency, HER2, menopause, cancer stage and obesity, only the association of obesity with shorter OS was at the borderline of statistical significance (p=0.067).

DISCUSSION

Some recent publications have suggested that obese women with breast cancer have a poorer response to chemotherapy. Subjects with higher BMI less frequently achieve pCR to chemotherapy (13). Whereas, it was proved that patients who achieve pCR have longer overall survival times (14). In the study presented above, obesity was associated with slightly lower rate of pCR1 response to chemotherapy (univariate analysis, association at the borderline of statistical significance, p=0.057). Obesity was an independent factor associated with a lower chance of achieving pCR1 in the entire study group and in the subgroup with determined HER status (association at the borderline of statistical significance). The relationship between BMI and achievement of pathological complete response (pCR) was not proved, which could have been associated with the small size of the study group. Many publications suggest that higher BMI is associated with poorer pathological response to induction therapy (13, 15, 16). A study by Litton et al. with a group of 1,169 breast cancer patients treated with neoadjuvant chemotherapy proved that higher BMI is associated with lower likelihood of achieving pCR (15). Different results were obtained in a study by Kayung-Hun Lee et al. who did not demonstrate the relationship between obesity and high BMI with the achievement of pCR and survival of Korean women treated with neoadjuvant chemotherapy due to locally advanced breast cancer (17). On the other hand, multicentre studies evaluating the impact of BMI on the achievement of pathological response to induction chemotherapy in breast cancer showed a close relationship between obesity and pCR (13,18). Higher BMI was associated with a worse pathological response (13). These results could have been caused by the effect of obesity on the response to chemotherapy as well as by the reduction of cytostatics dose, which is a common practice in case of overweight and obese patients (19, 20, 21). In a large retrospective study, Griggs et al. demonstrated that overweight and obese patients more frequently received reduced doses of cytostatics compared to patients with normal body mass (22). Medicine doses are reduced more frequently in obese patients also due to severe comorbidities. Especially in hormone-independent cancers, the reduction of cytostatic doses adversely affects results of oncological treatment (23).

The latest publications indicate a significant effect of obesity on pharmacokinetics of some cytostatics (24). However, there have been only few pharmacokinetics studies in obese subjects and data on pharmacokinetic parameters of most medicines in obese patients are lacking. Most frequently observed effects include an increase in the volume of lipolytic drugs distribution, change in the clearance of drugs and influence on the drug–protein binding process (25). Obesity is reported to be associated with the increase in the activity of cytochrome P-450 isoenzyme CYP2E1, decrease in CYP3A4 activity and increased elimination of drugs from the system (25). In everyday practice, doses of cytostatics are calculated per m² of body area, using body surface area (BSA) index. In obese subjects with BSA over 2 m², drug doses are very often reduced (26). Recent studies evaluating the behaviour of oncologists confirm that it is still usual practice to reduce drug doses in obese patients (27), which may lead to worsening of oncological treatment results (28). Patients with locally advanced breast cancer subjected to induction chemotherapy in the Department of Chemotherapy between 2001 and 2006 received doses of drugs calculated based on their
current BSA. Routine procedure in case of BSA > 2 m² was the reduction of cytostatic doses to the dose for BSA=2 m², and reduction of drug doses to 80% in patients with a history of internal diseases. Patients who developed toxicity to the treatment after the first cycle received 80% of the due dose in the next cycle.

In the presented studies, obesity was an independent factor associated with shorter DFS (association at the borderline of statistical significance, p=0.08). Obesity was an independent significant factor associated with shorter overall cancer-related survival (p=0.047). Menopause, on the other hand, was an independent significant factor associated with longer OS (p=0.029).

According to literature data, high BMI affects shorter survival time in postmenopausal (29,30) as well as premenopausal (29,30) women with breast cancer. A metaanalysis of 43 studies from 1963–2005 conducted by Protani et al. showed shorter overall survival time of obese patients, especially premenopausal women with breast cancer compared to patients with this cancer but normal body mass (29). OS is also affected by the type of further treatment, selected postoperative chemotherapy and hormone therapy.

**CONCLUSIONS**

1. Obesity appears to be an independent adverse factor associated with the failure to achieve pathological response pCR1 in patients with locally advanced breast cancer treated with AT neoadjuvant chemotherapy, but the association observed at the borderline of statistical significance requires confirmation in larger patient groups.

2. Obesity is a significant independent risk factor associated with shorter OS in patients with locally advanced breast cancer treated with AT neoadjuvant chemotherapy.

REFERENCES


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