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Adjuvant chemotherapy for early-stage breast cancer patients — daily clinical practice in selected cancer centres in Poland

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Background. Adjuvant chemotherapy for high-risk early-stage breast cancer patients significantly improves long-term treatment results. The decision to administer chemotherapy is made based primarily on prognostic factors (defined by the pathological characteristics of the primary tumour and regional lymph nodes) and also on patient-related factors, such as age, menopausal status and comorbidities. The guidelines on adjuvant chemotherapy have been established and reviewed for many years by several medical societies (NCCN, ESMO, PTOK, PUO) and experts of St. Gallen International Breast Cancer Conference. The aim of this study was to assess the pattern of adjuvant chemotherapy administration that had been routinely prescribed in four cancer centres in various regions of Poland (Opole, Kraków, Białystok, Poznań).

Methods. 218 early-stage breast cancer patients treated in selected cancer centres during 3 consecutive months of 2014 have been included in the analysis. The medical charts of the patients have been carefully evaluated. Data on the adjuvant chemotherapy administration have been reviewed retrospectively.

Results. The percentage of IHC tests in the analysed group was satisfactory. As much as 8 different chemotherapy regimens have been recorded. 98% of patients received anthracycline-based chemotherapy. Almost half of the patients (48.6%; 106/218) received taxanes. However, up to 27% (30/111) of patients with involved lymph nodes (pN+) did not received taxanes in the adjuvant setting. Trastuzumab was most frequently administered sequentially, which may be considered suboptimal.

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Key words: adjuvant chemotherapy, early-stage breast cancer, anthracyclines, taxanes, trastuzumab

Introduction

Since the 1990s there has been an observable decrease in breast cancer mortality rates in the countries of Western Europe and North America. This has been made possible thanks to improvements in early diagnosis, improvements in the efficiency of regional treatment as well as improvements in the efficacy of systemic treatment, including adjuvant chemotherapy.

The history of surgical treatment of breast cancer is more than 100 years long, yet it has also been known for a very long time that disease recurrence occurs even in cases of very extensive surgeries. The introduction and development of chemotherapy in the 1950s and 1960s resulted in the development of the concept of systemic treatment as a follow-up therapy after the surgery.

The history of clinical studies concerning adjuvant chemotherapy completing surgical intervention goes back to 1950. The first attempts with the use of thioTEPA and 5-fluorouracil consisted in perioperative chemotherapy that lasted for a few days [1]. The cancer cells which enter the circulatory system were then treated as the main source of the cancer's spread. It was shown in 1968 that in premeno-

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pausal patients, the application of this method allows for a significantly longer survival period [2]. A decisive influence on the current face of chemotherapy was obtained thanks to the results of two studies from the beginning of the 1970s. In the first of them, carried out by the American group, NSABP (National Surgical Adjuvant Breast and Bowel Project) among women with metastases to axillary lymph nodes (N+ status), the effectiveness of a 2-year adjuvant treatment with melphalan was evaluated (the cycles were repeated every 6 weeks for 2 years or until the progression) in comparison with surgery alone [3]. The study showed a statistically significant prolongation of the time to recurrence of the disease with the application of chemotherapy and this effect was most clearly seen in women below 50 years of age. In this group also the prolongation of the overall survival period was observed, yet the difference was not significant. Benefits related to chemotherapy was also observed in post-menopausal patients, yet the differences were not statistically significant. At the same time, in Italy, Bonadonna et al proved that post-operative chemotherapy with the CMF regimen allows prolongation of the time before the disease's progression, in particular in the group of patients with metastases to more than three axillary lymph nodes. After three years of the follow-up period, the share of deaths caused by the cancer in the chemotherapy group was 10.4%, whilst in the control group this share was 21.4% [4, 5]. The CMF regimen soon become a standard in the treatment of women with N+ status, in particular in the group of pre-menopausal patients. The data from this study were monitored in the next years which allowed confirmation that the benefits of such treatments persist during the longer follow-up period [6]. In the years following the adjuvant treatment of patients with early breast cancer, anthracyclines and taxoids were introduced.

From the 1970s onwards, dynamic progress in the clinical studies concerning the treatment of early breast cancer resulted in a large inflow of data. In order to systematise knowledge in this area, in 1983, at Oxford University, a group dealing with this issue was set up (Early Breast Cancer Trialists' Collaborative Group, EBCTCG). Initially the group comprised several dozen specialists, but today this group consists of a few hundred investigators worldwide. The group, since its creation, has been gathering data from clinical studies concerning early breast cancer and regularly publishing the results, every 5 years, since 1985. These data offer a general perspective of varied treatment approaches in non-advanced breast cancer. The recent analysis comes from 2010 and was published in 2011. It comprised the histories of 101 patients with non-advanced breast cancer participating in clinical studies in 1973–2003 [7]. In patients with early breast cancer, the improvement in results was the effect of the application of adjuvant chemotherapy as opposed to the lack of such treatment; moreover the improvement could be attributed to the addition of taxoids to the regimens based on anthracyclines and the standard use of larger anthracycline doses in comparison with CMF (Tab. I).

Table I. The comparison of various chemotherapy regimens in the adjuvant treatment of breast cancer

ER+ and ER– study group	RR	2p
CMF vs without CHT	0.76	< 0.0001
CAF vs without CHT	0.64	< 0.0001
4AC/EC vs without CHT	0.78	0.01
4AC vs CMF	0.98	0.67
CAF/CEF vs 4AC	0.78	0.0004
Antra→Tax vs Antra ≤ 240	0.86	0.0005
Antra→Tax vs Antra > 240	0.94	0.33

Some detailed recommendations are being created and updated on the basis of the current results of the studies. In the United States, the recommendations of the NCCN are binding, whilst in Europe — it is the consensus of the St. Gallen conference, organised every two years. American and European recommendations are not always compliant with each other, which is also the case with other cancers. Polish recommendations are made according to the St. Gallen consensus. Currently systemic treatment concerns the majority of breast cancer patients.

The decision to introduce systemic adjuvant treatment should be based on the evaluation of individual risk of recurrence (prognostic and predictive factors) and the probability of benefit from the application of a given method. It is necessary to take into consideration predicted adverse effects, the performance status of the patient and her preferences as well as the comorbidities. Now it is the beginning of an era of genetic tests which are meant to support us in increasing best selection of adjuvant therapy for specific patients. There are no definitively perfect solutions. Many patients are treated in a suboptimal way and many unnecessarily, as only 15% of patients with pN0 status have recurrence of the disease, whilst 50% of such patients undergo chemotherapy.

The objective of the study

The objective of the work was to evaluate the treatment algorithm in the application of adjuvant chemotherapy in everyday clinical practice in 4 selected oncology centres in diverse regions of Poland — Opole, Kraków, Białystok and Poznań.

Materials and methods

A retrospective analysis of adjuvant chemotherapy applied in a group of 218 patients with early breast cancer was performed on the basis of medical documentation. These were the patients treated in each of the centres within 3 consecutive months in 2014.

Table II. Pathological and clinical characteristics

Property	Total n = 218	Centre 1 n = 51	Centre 2 n = 19	Centre 3 n = 48	Centre 4 n = 100
Age (years)					
median	56	51	45	60	57
scope	(30–83)	(30–74)	(31–62)	(32–83)	(30–75)
Menopause					
before	117	30	11	14	62
after	71	21	8	34	8
no data	30	0	0	0	30
Histological type					
ductal	200	43	17	45	95
lobular	8	4	1	2	1
others	10	4	1	1	4
Histological grade					
G1	5	0	0	0	5
G2	88	19	3	25	41
G3	119	28	16	21	54
no data	6	4	0	2	0
Metastases to axillary lymph nodes					
0	107	23	10	29	45
1–3	54	16	3	12	23
4 and more	57	12	6	7	32
Ki67					
no data	31	0	1	30	0
< 21%	37	5	7	10	15
> 21%	150	46	11	8	85
Oestrogen receptors					
positive	150	29	12	38	71
negative	59	21	3	10	25
no data	9	1	4	0	4
Progesterone receptors					
positive	128	24	10	35	59
negative	78	25	3	13	37
no data	12	2	6	0	4
HER2 receptor					
0	59	16	7	21	15
1+	64	4	6	14	40
2+ (FISH performed)	33 (30)	11 (11)	3 (2)	3 (3)	16 (14)
3+	62	20	3	10	29
No data	0	0	0	0	0

All the patients underwent primary surgical treatment followed by chemotherapy, and the patients with neoadjuvant treatment, patients with infiltrating cancer and patients in whose cases adjuvant chemotherapy was abandoned were excluded from the analysis. The groups were quite diversified with regards to the specific centres. The age median in the entire group of patients was 56, yet there were quite significant differences between the centres (Tab. II). In all the analysed patients, the complete results of histopathological examinations and immunohistochemistry (IHC) tests, determining the expression of the oestrogen receptor (ER), progesterone (PgR) and HER2 expression were available. The dominating group of cancers were ductal, both moderately and poorly differentiated, in more than 50% of cases the cancers showed the expression of steroid receptors, whilst in about 5% of cases within the group, the steroid receptor status was not known.

Table III. Adjuvant treatment

Property	Total n = 218	Centre 1 n = 51	Centre 2 n = 19	Centre 3 n = 48	Centre 4 n = 100
Chemotherapy					
1 — FAC/FEC	19	17	2	0	0
2 — 6xCMF	2	0	0	1	1
3 — TAC	12	11	0	1	0
4 — 4 × AC/EC	90	9	6	32	43
5 — 6 × AC	1	0	0	0	1
6 — antra→pct q1	51	3	2	0	46
7 — antra→dct q3	42	10	9	14	9
8 — other (what?)	1	1-TCH	0	0	0
Trastuzumab					
without	156	25	17	40	74
after CHT	36	16	2	8	10
with taxoids	21	5	0	0	16
clinical study	5	5	0	0	0
Clincial studies	5/218	5/51	0/19	0/48	0/100
T in HER2+ (IHC/FISH)	75 (62/13)	28 (20/8)	3 (3/0)	12 (10/2)	32 (29/3)
without	14	2	2	4	6
after CHT	41	22	1	8	10
concurrently with taxoids	19	3	0	0	16
clinical study	1	1	0	0	0

The HER2 receptor was determined in every case, and in the patients with inconclusive results of the IHC test (HER2 2+), in 90% of cases, the amplification was tested with the FISH method. HER2 positive breast cancer was diagnosed in 75/218 patients, which makes up 28% of the study group, whilst in 62 patients the gene amplification was found with the ICH test method and in 13 cases — with the FISH test.

In half of the patients (50.9%; 111/218), metastases to axillary lymph nodes were found (pN+ status). Proliferation marker Ki-67 was not determined in 30% of patients.

Results

In the study group, 8 different chemotherapy regimens were used (Tab. III). Almost in all the patients (98%), anthracyclines were administered. Most frequently this treatment consisted solely in 4 chemotherapy cycles with anthracyclines — 4 AC (up to the doxorubicin dose of 240mg/m^2) or 4 × EC. Such treatment was administered in 41% of cases (90/218). Only 2 patients were given CMF regiment and 1 patient — TC, or rather TCH regiment and this patient was treated within a clinical trial.

Taxoids were administered to almost half of the patients (48.6%; 106/218), yet in one centre this rate was significantly lower. There were two regimens used with almost an equal frequency — 4 cycles of docetaxel every 3 weeks and 12 weekly cycles of paclitaxel. Yet the application of taxoids was not completely compliant with the pN+ status, although this was the situation in the majority of cases. In some cases, these drugs were administered in patients with pN0 status, and in some cases, in spite of the presence of metastases in the axillary lymph nodes, taxoids were not administered (Fig. 1, numeric graph). 27% (30/111) of patients with a pN+ status did not receive taxoids in adjuvant treatment.

No treatment with paclitaxel, in doses every 3 weeks, was used in adjuvant therapy and also no application of platinum-based chemotherapy was observed.

HER2 positive breast cancer was diagnosed in 75/218 patients, making up 28% of the study group; in the same group, 14 patients did not receive trastuzumab: in 2 cases due to cardiological contraindications and in 12 cases — by the size of the primary tumour below 1 cm, which is the inclusion criterion in the drug prescription programme. In the majority of cases, trastuzumab was administered sequentially after the completion of chemotherapy, whilst concurrent administration with taxoids was very rare (in two centres this method was not used at all).

Discussion

The introduction of systemic adjuvant treatment has changed the face of the natural history of breast cancer, first of all by means of a significant decrease in the frequency of the occurrence of distant metastases. As a result, the chances of curing patients with early breast cancer have increased [8]. The analyses performed by EBCTCG clearly

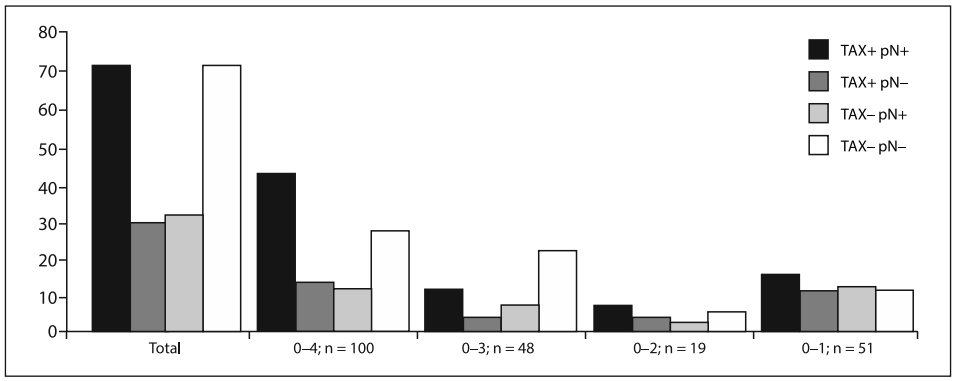

Figure 1. The use of taxoids, depending on the number of metastases in axillary lymph nodes

showed that chemotherapy prolongs the time of survival, in particular in the patients below 50 years of age [7, 9]. Within the 40-year history of this method of treatment a few significant landmarks have been observed (the introduction of polychemotherapy, CMF regimen, anthracyclines, taxoids, Trastuzumab), but still the basic challenge of the individualisation of treatment, remains i.e. the selection of the appropriate treatment methods for specific patients.

None of the centres participating in the study is dedicated to a specific age group, but some centres treat the patients who are younger than the average population. Perhaps in some regions of Poland, the migration of young people leads to the fact that we treat an older population. This analysis does not explain such differences, as it covers solely a period of 3 months, and the groups of patients might differ with regards to their number.

In more than half of the patients treated with adjuvant chemotherapy, the expression of steroid receptors in the tumour was found. The patients with positive oestrogen receptors constitute a very heterogenous group with varied levels of the HER2 receptor expression or differentiated Ki67 levels. As is shown by earlier quoted analyses, significant benefit of the use of adjuvant chemotherapy is seen in this group [7]. In about 5% of patients in the entire group, no data on the steroid receptors status were available, which is quite disturbing as it is necessary for the decision on whether or not to introduce adjuvant therapy. In all the patients the HER2 receptor status was determined, and, in the case of inconclusive results of the IHC test (Her2 2+), the FISH test was performed in almost all of the cases (90%). The Ki67 status is currently regarded as a necessary diagnostic element. In spite of many doubts concerning the threshold value of this indicator, it is still very important for the determination of the immunochemistry subtype [10]. It may provide additional grounds for the application of chemotherapy in such patients in the case of moderately dif-

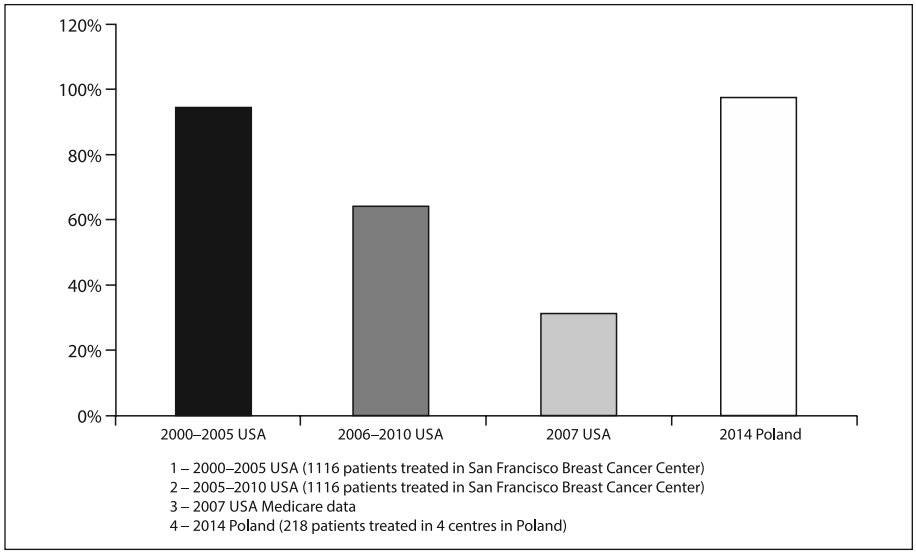

Figure 2. The rate of patients treated with adjuvant anthracyclines

ferentiated cancer with the expression of steroid receptors,. In the studied group, the Ki67 status was not determined only in the case of patients with poorly differentiated cancer, G3, so thus it did not have any influence on the selection of the adjuvant systemic therapy.

The majority of the regimens proposed in the recommendations for adjuvant chemotherapy are based on anthracyclines, yet the deviation from the application of anthracyclines is a valuable method, which may be taken into consideration in a group of patients with an increased risk of cardiotoxicity, so those in whose case there is a comorbidity of not only a reduced left ventricle ejection fraction (LVEF), but also hearth ischaemic disease, a long history of arterial hypertension or poorly controlled one, obesity, lipid metabolism disorders, DM or tobacco smoking. The study comparing 4 AC chemotherapy cycles and 4 cycles of docetaxel with cyclophosphamide (TC) showed that treatment with the TC regimen was connected with an improvement in the progression free survival and overall survival rate and the benefit continued throughout a many-year follow-up period [11]. The TC regimen was characterised with a different adverse reaction profile. In the population of the patients with HER2 positive breast cancer, the value of the treatment with exclusion of anthracyclines was confirmed, also over a many-year-long follow-up period [12]. Such treatment is safer for the circulatory system.

In the study group, anthracyclines were administered in more than 95% of patients. In other countries, though, the application of the drugs from this group is becoming less and less common in the adjuvant treatment of the breast cancer (Fig. 2) [14].

In the presented group, in the majority of patients in whose case the regimen with anthracyclines and taxanes was applied the AC → T sequential therapy was the method of treatment. The TAC regimen was applied only in 5.5% of patients from the entire group. In one of the centres, however, this method of treatment was applied in 20% of patients. This may be indicative of the fact that the choice of the treatment regimen is also influenced by some other, non-medical factors. Treatment according to the TAC regimen is shorter and requires fewer visits to the oncology centre. The efficiency of both methods is comparable, with the application of G-CSF (granulocyte colony-stimulating factor) within the TAC therapy; whereas the toxicity is also comparable [14].

What is important the treatment according to the regimen providing for 6 courses of AC was administered only to 2 patients, so this was less than 1% of the entire group. Until recently in many centres in Poland, such treatment had been commonly used. The cardiotoxicity risk connected with the application of the standard doxorubicin doses (up to 240 mg/m^2, and thus 2 courses of treatment in the AC regimen) is 2–3%. The application of a higher dose of conventional doxorubicin increases the risk of iatrogenic heart failure [15].

The very rare use of the treatment according to the CMF regimen raises some concern. This "classical regimen" of adjuvant treatment, introduced 40 years ago, was replaced in the 1980s by newer drug combinations containing anthracyclines and taxanes [4]. It seems however, that in some clinical situations, for example in patients with contraindications for the use of anthracyclines and with a low risk of recurrence (N0), treatment with the CMF regimen can still be used. There are also reports pointing to a higher efficacy of this regimen in the group of patients with tumours without the steroid receptors expression and without the overexpression of the HER2 receptor. In the presented group, the majority of patients were younger women in pre-menopausal age. In this group, however, there were also women above 70 or 80 years of age, and the CMF regimen was applied only in 2 cases. This is probably the result of a conviction about the superiority of 4 AC cycles over 6 CMF courses, whilst the efficiency of these 2 courses is comparable [16].Observation over many years confirms the safety and persisting efficacy of the treatment according to the CMF regimen [17].

In the study group no dose dense chemotherapy was used. Such a method of drug dosage has been the subject of studies for several years, and the results suggest that this may bring additional benefit in particular to groups of younger patients not burdened with comorbidities [18–22]. The current international recommendations (NCCN, St. Gallen, ESMO) allow for dose dense chemotherapy in particular in the population of patients with a high risk of recurrence (high Ki67 proliferation rate, triple negative breast cancer or B luminal cancer) [10, 23, 24].

In the study group, the sequential administration of Trastuzumab, after the completion of chemotherapy was dominant. A number of studies suggest more benefits in the concurrent use of Trastuzumab with taxoids. The survey carried out among oncologists confirms that currently this is the most common practice in Europe [25]. 97% of participants of the consensus panel at the St. Gallen conference were in favour of such therapeutic management [10]. Current regulations in Poland related to the reporting and settlement of the drug programme, however, reduce the possibilities of this way of treatment.

Conclusions

The development of adjuvant therapy significantly affects the decrease of breast cancer mortality. No standard in adjuvant therapy is perfect, however, and breast cancer is a diversified disease, so larger individualisation of adjuvant therapy is possible.

The collected material points to the common use of anthracyclines in the adjuvant treatment. Some of the patients with metastases to axillary lymph nodes were not receiving

taxoids. Trastuzumab was most frequently administered sequentially, which is not an optimum management. The studied group was not representative, yet it reflected the everyday practice throughout many regions of Poland.

This is a pilot study. The authors are considering the invitation of other investigators from other Polish centres and plan to broaden the analysis with regards to the immunohistochemistry subtypes and the choice of adjuvant chemotherapy.

Conflict of interest: none declared

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