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CLINICAL STUDY

How can an immunologist influence the occurrence of secondary infections in breast cancer? Real-life study

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ABSTRACT
BACKGROUND: Clinical manifestation of secondary immunodeficiency is responsible for the decrease in life quality in cancer-treated patients, which may result in administration delays, dose reductions, even in discontinuation of treatment. The main aim of presented study was to stress the possibility of influencing secondary infections with adjunctive immuno-regulatory medicament (AIRT).
METHODS: The presented real-life retrospective study involved a cohort of 94 adult female patients aged from 30 to 87 years with mean age of 58.4 (SD = 11.37). The cohort was divided into two groups. One group (54 patients; 57.45 %) was treated by using the adjunctive immuno-regulatory medicaments and the other, control group (40 patients; 42.55 %), was without any immunological interventions in relation to secondary immunodeficiency. Patients in both groups were treated by standard oncotherapy.
RESULTS: The results show that in patients who were sent for immunological consultation, double incidence values of mild secondary infection frequencies were revealed. When immunologists decided to add adjunctive immunomodulatory medicament, the occurrence of infection and consumption of antibiotics decreased. The decrease was significant in the second evaluated interval (6th – 12th month).
CONCLUSIONS: Our results strongly advise regular or even preventive examination of cancer patients by immunologic specialist for the purpose of attenuating some negative consequences of applied anti-tumor therapy *(Tab. 1, Fig. 4, Ref. 14)*. Text in PDF *www.elis.sk*
KEY WORDS: secondary infection, breast cancer, real-life study, clinical immunology, treatment.

Introduction

According to worldwide epidemiological statistics, breast cancer in women is classified as the most common malignancy which causes more than half a million deaths annually worldwide (1). From the pathophysiological point of view, malignancies represent a breakdown of immunological mechanisms and a number of experimental and clinical observations have provided evidence supporting the notion of tumor immune surveillance in humans (2). Indeed, also antitumor therapy (radiation, chemotherapy, targeted immunotherapy, hormonal therapy) can be complicated by the presence of secondary immunodeficiency. Clinical manifestations of immunodeficiency (3) are responsible for the decrease in the quality of life in treated patients. Such immune malfunction may result in administration delays, dose reductions, discontinuation of treatment, and even death (4).

The fact that during anti-tumor treatment, several infections may be mistaken for acute and/or late therapeutic effects, and thus lead to less-than-optimal treatment decisions, makes the knowledge of this problem even more relevant (5). Breast cancer chemotherapy is associated with long-term changes in immune parameters that should be considered during the clinical management (6). The study by Verma et al has demonstrated that the adaptive immune system is altered following chemotherapy for at least nine months after therapy. A similar result on systemic immune response in breast cancer patients after adjuvant radio-chemotherapy was published by Mozaffari et al (7).

According to many literary sources several infections such as reactivation of TBC, anaerobic and atypical bacterial infections, as well as Gram negative commensal bacterial infections occur as a side effect of various treatment modalities. Etiological causes also include viruses (HSV, RSV, CMV influenza virus A/B) and fungi (e. g. *Candida sp., Aspergillus, Pneumocystis*). Although most infections are caused by bacteria, especially by Gram-negative species, viruses are being increasingly identified (3). Infections are quite different from those seen in patients with hematologic malignancies, especially with neutropenia, and have generally been less well studied. Recent data regarding many aspects of such infections are scant (8). Brand et al (9) presented a

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prospective population-based study of 8,338 women with stage I–III breast cancer in the Stockholm area diagnosed in 2001–2008. Out of the evaluated cohort, 720 women had an infection-related hospitalization and the great majority of these events occurred during the first year.

The increased susceptibility to infections results from intensified anti-tumor therapy. Complications related to infection or reactivation of endogenous latent may compromise the benefits of treatment alone. It is usually caused by dysregulation of immune homeostasis, and such a state increases the risk of secondary infections (10). Various studies show serious secondary infections after radiation or chemotherapy, but none of them evaluates even a possibility that adjunctive immuno-regulatory treatment (AIRT) could have an effect on them.

The reason for providing our real-life retrospective study lies in the fact that we have not found any study reporting on prevailing community-acquired infections in breast cancer patients treated with basic antimicrobial/antibiotic therapy in combination with adjunctive immuno-regulatory medicament at out-patient units by general practitioners or first-line specialists in otorhinolaryngology, pneumology, immuno-allergology, dermatology, or infectiology.

The main aim of the study was to evaluate the occurrence of consecutive infections throughout and after oncotherapy in breast cancer patients. The second aim was to estimate the effect of immunologic intervention on the incidence of these infections and point out the need for proper/preventive immunologic diagnostics and subsequent adjunctive immuno-regulatory treatment.

Patients and methods

General characteristics of the participants

Presented real-life retrospective study involved a cohort of 94 adult female patients aged from 30 to 87 years with mean age of 58.4 (SD = 11.37). Data were collected from twelve clinical immunology centers and one oncology center. The cohort was divided into two groups. One group (54 patients; 57.45 %) was treated by using the adjunctive immuno-regulatory medicaments and the other, a control group (40 patients; 42.55 %), had no immunological interventions owing to related secondary immunodeficiency. Patients in both groups were treated by standard oncotherapy. The first group further consisted of 40 (74 %) patients who went to see an immunologist during the treatment of their primary oncologic diagnoses which led to secondary infections that did not require admission to hospital. Of them, 14 patients (26 %) visited a specialist for a different reason (regular follow-up, allergy, etc.) and 17 (31.5 %) females underwent clinical immunologic examination as recommended by clinical oncologists. All obtained data were summarized from available medical records taken from involved centers.

Family history of the patients

Out of 94 records, 41 patients (43.62 %) had a positive family history of cancer, of which 14 (14.89 %) patients had a history of breast cancer. A negative family history occurred in 42 (44.68 %) patients while in 11 patients (11.7 %), no family history was available.

Cohort characteristics according to immunologic intervention

For immunologic intervention, we considered an administration of peroral or parenteral drugs registered as nationally authorized medicinal products (azoximer bromide, inosine praenobex, human dialyzable leukocyte lysate). The control group consisted of 40 patients to whom no adjunctive immuno-regulatory medicament was added to the treatment of the oncological diagnosis.

Data collection

Frequency of infections during the first and control examinations at the immunology or oncology centers was recorded. Obtained data were collected gradually in several steps at individual centers from patients' medical records after providing comprehensive input information necessary for granting voluntary patients' consent for data collection and processing in accordance with applicable legislation (GDPR) and principles of good clinical practice (GCP – ICH EG, rev2). In order to maintain anonymity, numerical codes were assigned to patients after enrollment and obtained data were subsequently added only to an extent obtained in the medical records.

The first period (0–6th month) was determined to take a span of 6 months from the date of malignancy confirmation, and to include two visits to the immunologist at the beginning and end of the evaluated period. The second period (6th–12th months) spanned between the sixth month and 12th month after the initial visit was determined based on regular semi-annual medical check-ups at the immunologist´s office. Selected intervals correspond with the known literary data (9). Acquired data included the incidence of infections and consumption of antimicrobial therapy.

Statistical analysis

Initial procedure-describing data were summarized in form of frequency tables and charts. Then, the analysis was based on comparison of the treatment and control groups data on the incidence

Tab. 1. Demographic data and tumor characteristics.

All cohort	94 (100%)
AIRT patients	54 (57.45%)
Controls	40 (42.65%)
Median age (range)	58.4 (30–87)
Tis	4 (4.3%)
T1	33 (35.1%)
T2	33 (35.1%)
T3	2 (2.1%)
T4	4 (4.3%)
Unspecified	18 (19.1%)
N0	71 (75.5%)
N1	23 (24.5%)
M0	89 (94.7%)
M1	5 (5.3%)
Grade 1	7 (7.44%)
Grade 2	75 (79.8%)
Grade 3	12 (12.76%)
Grade 4	0

of health problems and possible selected clinical indicators using Pearson's chi-square test for categorical variables and Student's t-test, or Mann-Whitney U-test for continuous variables depending on the normality of the value distribution. Paired samples t-test was used for analyzing changes in time in patients. All data analyses were conducted using the statistical software package IBM SPSS 22.0.

Results

Our cohort consisted of 94 adult female patients with mean age of 58.4 years (SD = 11.37, 30–87 years). In the treated group, 54 patients (57.45 %) had taken AIRT in various regimens according to their immunologists´ decisions. One subgroup (17 patients) received treatment preventively, i.e., before starting the oncologic procedures. In this subgroup, only parenteral administration was applied. The control group consisted of 40 cancer patients (42.55 %) of whom 30 (75 %) were from the oncology center. The oncologists had no need to ask for an immunologic intervention. Ten (25 %) patients were from immunologic centers, however, there was no need to prescribe immunologic interventions due to cancer-treatment-related secondary infections. Demographic data and tumor characteristics of the evaluated cohort are shown in Table 1.

We recorded that in AIRT group, the frequency of infections in cases of parenteral or peroral administration reached approximately the value of 3 infections in the first period and decreased to approximately one infection in the second period. Indeed, in the control group, the frequency of infections did not reach even a value of one infection in either of periods (average 0.43 and 0.78). In both treated groups (parenteral and peroral) a statisti-

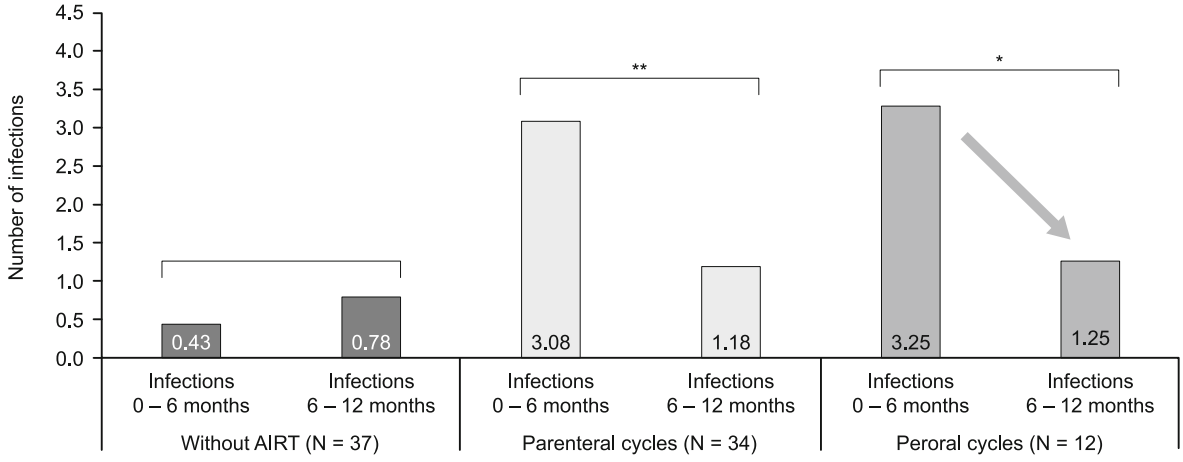

Fig. 1. Comparison of the difference in average number of infections in two time periods (0–6th vs 6th–12th month) among three groups of patients, i.e., patients without AIRT, those undergoing parenteral cycles of AIRT and those undergoing peroral cycles of AIRT.

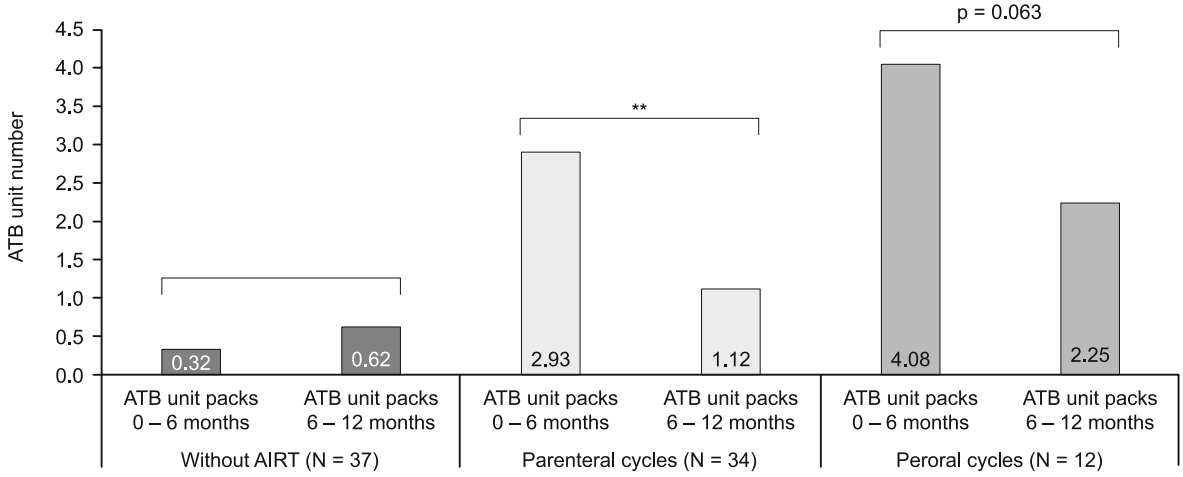

Fig. 2. Comparison of the difference in average of prescribed unit packs of antibiotics in two time periods (0–6th vs 6th–12th month) among three groups of patients, i.e., patients without AIRT, those undergoing parenteral cycles of AIRT and those undergoing peroral cycles of AIRT.

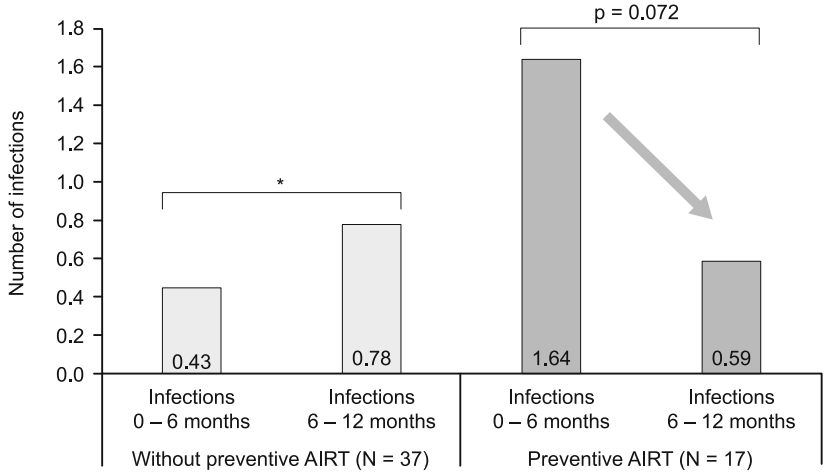

Fig. 3. Comparison of the difference in average number of infections in two time periods (0–6th vs 6th–12th month) among patients with preventive AIRT and those without preventive AIRT.

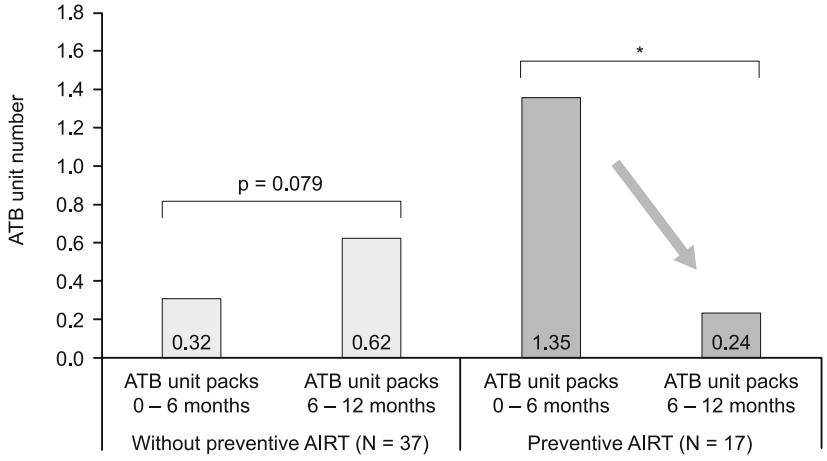

Fig. 4. Comparison of the difference in average of prescribed unit packs of antibiotics in two time periods (0–6th vs 6th–12th month) among patients with preventive AIRT and those without preventive AIRT.

cally significant decrease in infections was recorded during the second period (Fig. 1).

When evaluating the consumption of antibiotics (in unit packs), the analyzed sample showed a decrease in prescribed antibiotics during the second period of observation in both treated groups, while in the control group, the change in antibiotic consumption was not significant (p = 0.05, p = 0.063, respectively) (Fig. 2).

The most surprising results were obtained as a result of analyzing a subgroup of treated patients who received treatment preventively prior to the start of oncologic procedures (17 patients). As seen from the following figures, the decreasing trend in the frequency of secondary infections reached the statistical significance threshold (p = 0.07) (Fig. 3), even a statistically significant decrease in the use of antibiotics was recorded (Fig. 4). Yet, as shown in Figure 4, a slightly increasing trend was reported in the control group. It is necessary to emphasize that except for one person, all other 16 patients in the preventive subgroup were treated by intramuscular injections of azoximer bromide.

Discussion

Currently, the main accepted approach for treating breast cancer involves breast-conserving surgery, adjuvant radiotherapy, chemotherapy or a combination of them (11). Despite intensive research, the exact impact of such treatment regimens on the immune system is less known and neither is the effect of adjunctive immuno-regulatory treatment. Vento et al. reported higher susceptibility to infections after chemotherapy, but he supposed that drug prophylaxis has a limited role in these patients (3).

A significant number of breast cancer patients are hospitalized with an infection following the diagnosis, which in turn predicts a poor prognosis (9). But the knowledge of AIRT influence in patients not requiring hospitalization is poor. The presented study is the first published real-life study reporting on the effects after using the AIRT in cancer treatment especially in solid (breast) cancer patients not requiring hospitalization due to secondary infections. Patients requiring hospitalization, as reported by Brandt were not included in the presented cohort.

Our evaluation has shown that AIRT, if applied by way of parenteral or peroral administration, leads to a statistically significant decrease in the frequency of infections during the second period, i.e., during the sixth to twelfth month after determining the diagnosis and beginning of the complex treatment. Yet, the results were only on the border of statistical significance. Consumption of antibiotics (in unit packs) decreased approximately two-fold in the AIRT treated group.

We suppose that also oral administration of AIRT might influence the treatment of secondary infections, but the number of patients in the evaluated group was relatively small (12 patients). Therefore, it did not provide us with appropriate data. This small subgroup was treated predominately by inosine pranobex, but due to the size and considerable insufficiency of data, the subgroup was not analyzed.

The most surprising results were obtained as a result of a more profound analysis, namely by evaluating a subgroup of AIRT-treated patients (17 females) who received treatment preventively, i.e., prior to the start of subsequent oncologic procedures. Decreases in

secondary infections as well as in use of antibiotics have reached statistical significance ($p = 0.07$ and $p = 0.03$, respectively). Seventeen patients in the preventively treated subgroup received intramuscular injections of azoximer bromide which is registered in Slovakia as a nationally authorized medicinal product for the treatment of secondary immunodeficiency and therefore widely used by immunologists in this region.

Our results closely correspond to recently published data by Alexia (12) who observed the clinical effect of azoximer bromide in breast cancer patients by activation of cytotoxic lymphocyte response through dendritic cell maturation. The clinical use and safety profile of azoximer bromide was reported in post-authorization study on a heterogeneous population of patients, mostly with chronic recurrent bacterial or viral infections (13). Also, Powell et al (14) summarized, mainly based on Russian research, that the immunostimulatory effect, bactericidal activity, as well as antioxidant activity of azoximer bromide in the treatment of such infections require additional immunostimulation.

A weakness of the presented real-life retrospective study lies in the great variability and absence of uniform guidelines for the immunologic management of cancer patients. The heterogeneity of acquired data could have reduced the strength of evidence. Indeed, we have to emphasize that retrospective acquisition and analysis of outpatient medical records can bring about certain inaccuracies. It is important to stress out that our evaluation has documented the occurrence of mild or moderate secondary infections which did not require admission to hospital and were managed solely by oncologist or immunologist upon request.

Conclusion

Secondary infections quite often accompany modern intensive anti-tumor therapy. The results coming out from our real-life retrospective study show that in breast-cancer-treated patients who were sent for immunological consultation, double incidence of mild secondary infections were revealed. When immunologists decided to add adjunctive immunomodulatory medicament to antimicrobial treatment, the occurrence of infection and consumption of antibiotics particularly in parenterally treated group decreased. The decrease was markedly seen in the second evaluated interval (6th–12th month). In patients who were ordered to take adjunctive immunomodulatory drugs preventively, the decrease in infections frequency and antibiotic consumption reached the statistical significance. These results strongly suggest regular or even preventive examinations of cancer patients by immunologic specialists for the purpose of attenuating some negative consequences of applied anti-tumor therapy. The need for a prospective designed study concerning adjunctive immunomodulatory treatment not only in breast cancer patients is expected.

Learning points

- Adjunctive immuno-regulatory medication decreases occurrence of secondary infection and antibiotic consumption in breast cancer patients.
- Regular/preventive examination of cancer patients by immunologic specialists is advised.

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