Investigation of Clinical Course and Possible Drug Interactions in Patients with Multiple Sclerosis and Breast Cancer

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ABSTRACT

This study aims to investigate the clinical course and potential drug interactions of breast cancer patients diagnosed with multiple sclerosis (MS). Ten patients diagnosed with MS and breast cancer, who were followed up and treated in the authors' centre between January 2000 and December 2020, were retrospectively scanned from the Hospital's electronic registry system and included in the study. The patients' age, gender, history of MS diagnosis, drugs used, date of breast cancer diagnosis, stage at diagnosis, pathological features, treatment information, surgery types, recurrence or metastasis history and regions, and side effects observed during anticancer treatment were recorded.

Key Words: *Multiple sclerosis, Breast cancer, Drug-drug interactions.*

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INTRODUCTION

Multiple sclerosis (MS) is the most common inflammatory disease of the central nervous system (CNS). Two main mechanisms come to the fore in the pathogenesis of MS. These are demyelination accompanied by inflammation, astroglial proliferation (gliosis), and neurodegeneration. Tissue damage is limited to the central nervous system.[1]

MS is a significant cause of disability in the young adult population. The fact that the patients were diagnosed with concomitant cancer further complicates the situation since the chemotherapeutics to be administered to the oncology patients are significantly affected by the Eastern Cooperative Oncology Group (ECOG) performance score of the patients. In addition, since new treatments are on the agenda in the treatment of MS and these treatments are not frequently used medicines, possible drug interactions with cancer treatment taken simultaneously come to the fore. There is no study on drug-drug interactions of medicines for multiple sclerosis and antineoplastic agents. This study aimed to evaluate drug-drug interactions in the patients with MS and breast cancer.

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METHODOLOGY

Patients diagnosed with MS and breast cancer aged >18 years, who were followed up and treated in the Medical Oncology clinic between January 2000 and December 2020, were scanned retrospectively from the hospital electronic registry system. Patients younger than 18 years and those with secondary malignancy were excluded. Seventeen patients who met the criteria were identified. However, only 10 patients were included in the study since the records of 10 of these 17 patients could be accessed entirely. The patients' age, gender, history of MS diagnosis, drugs used, breast cancer diagnosis date, stage, neoadjuvant or adjuvant treatment information, surgery types, recurrence or metastasis history and regions, and side effects observed during anticancer treatment were recorded. SPSS 20.0 for Windows programme was used for statistical analysis. Categorical variables were given as numbers and percentages, and numeric variables were presented as mean ± SD.

RESULTS

All ten patients included in the were females. The mean age of the patients was 52 (±10.4) years. The youngest was 41 years, and the most geriatric patient was 67 years old. Six of the 10 patients were premenopausal and four were postmenopausal. All patients were non-metastatic at diagnosis. The TNM classification of the patients is explained in detail in Table I. The ECOG performance score were: 1 (3 patients), 2 (5 patients), and 3 (2 patients).

Considering the MS histories of the patients, the mean disease duration (time from diagnosis to the current date) was 17.7 years. The longest follow-up was 27 years, and the shortest was 12 years. Five patients received interferon beta 1, one patient

received fampridine, one patient received glatiramer acetate, one patient received ocrelizumab, one patient was under drug-free follow-up, and one patient was followed up with attack treatments, mostly corticosteroids because of the frequent attacks.

All ten patients included in the study had breast mass biopsy which was performed at the authors' centre. The patients' oestrogen receptor (ER) percentage, progesterone receptor (PR) percentage, human epidermal growth factor-2 receptor (HER2) status, Ki67 value, and grades are listed in Table II. *BRCA2* heterozygous mutation was detected in one patient. No *BRCA* mutation was seen in the other nine patients.

Table I: Pathological TNM stages and tumour sizes of patients.

	N stage	T stage	Tumour size (mm)	Stage
Patient 1	N1	T2	45	2B
Patient 2	N2	T3	54	3A
Patient 3	N1	T2	35	2B
Patient 4	N0	T1c	19	1A
Patient 5	N1	T1c	18	2A
Patient 6	N0	T2	30	2A
Patient 7	N2	T2	30	3A
Patient 8	N2	T3	80	3A
Patient 9	N0	T1c	20	1A
Patient 10	N1	T2	35	2B

Table II: Pathological characteristics of patients at the diagnosis.

	ER (%)	PR (%)	HER2 IHC score	Ki67 (%)	Grade
Patient 1	25	50	3+	70	3
Patient 2	0	0	0	40	3
Patient 3	100	60	3+	30	3
Patient 4	90	10	3+	60	Unknown
Patient 5	90	0	0	20	2
Patient 6	0	0	3+	30	3
Patient 7	100	5	3+	25	2
Patient 8	90	1	2+ (SISH-)	60	2
Patient 9	1	2	3+	80	3
Patient 10	60	5	3+	Unknown	3

ER: Oestrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor-2 receptor, IHC: Immunohistochemistry, SISH: Silver in situ hybridisation.

Neoadjuvant chemotherapy was given to one patient, and adjuvant chemotherapy was given to the other nine patients. Since the patient who received neoadjuvant therapy was HER2 positive, she received four courses of adriamycin and cyclophosphamide (AC), followed by four courses of docetaxel, trastuzumab, and pertuzumab. After four courses of AC in two patients and then 12 weeks of paclitaxel, four courses of AC followed by trastuzumab with paclitaxel for 12 weeks, four courses of AC in two patients, followed by four courses of docetaxel and trastuzumab and one patient with three courses of cyclophosphamide, epirubicin, and 5-fluorouracil. One patient was given trastuzumab emtansine (T-DM1). Grade 3 neutropenia developed in four patients, and Grade 2 peripheral neuropathy in one patient. It was determined that this situation did not prevent the completion of chemotherapy in the patients who developed toxicity, and all of them completed their adjuvant or neoadjuvant treatments. Except for chemotherapy-related side effects, it was observed that one patient could not complete the adjuvant therapy due to infection.

Nine patients were followed up without recurrence after the completion of the treatment. One patient aged 42 years, developed a recurrence of liver metastasis 22 months after the end of adjuvant therapy. She had been followed up with the diagnosis of MS for 27 years and was currently receiving fampridine treatment. At diagnosis, the stage was IIIA, and the hormone profile was triple-negative.

All patients underwent breast surgery. In the radiotherapy evaluation, seven out of 10 patients received adjuvant radiotherapy.

The chemotherapy regimens that the patients received and their treatments for MS were examined in terms of drug interactions and treatment toxicity. It was determined that none of the patients experienced drug interactions related to MS treatments during the period they received chemotherapy. In addition, there was no increase in the frequency of multiple sclerosis attacks or exacerbation of the disease during chemotherapy periods. Chemotherapy tolerances were good. Except for neutropenia and peripheral neuropathy, no chemotherapy-related significant toxicity was detected.

DISCUSSION

The first treatments used in the treatment of MS are interferons and glatiramer acetate.[2] IF beta is an immunomodulator that decreases proinflammatory cytokines, increases anti-inflammatory cytokines, downregulates MHC expression in antigen-presenting cells, and inhibits T cell proliferation.[3] Glatiramer acetate is an agent that acts by balancing regulatory cytokines and proinflammatory cytokines.[4]

New treatment options have also been added to the process. Natalizumab is a monoclonal antibody that inhibits lymphocyte migration to the CNS by inhibiting the adhesion molecule α4β1 integrin on the lymphocyte surface.[5] Sphingosine-1-phosphate (SIP) receptor modulators such as fingolimod, siponimod, and ozanimod act by causing the sequestration of lymphocytes in primary lymphoid organs.[6,7] Treatments with anti-CD 20 monoclonal antibodies such as rituximab and ocrelizumab are also considered among the treatment options considering humoral immunity in the pathogenesis of the disease.[8,9]

In the treatment of breast cancer, chemotherapeutics that are frequently used in clinical practice are mainly adriamycin and epirubicin, which are in the anthracycline group, cyclophosphamide, an alkylating agent, paclitaxel, and docetaxel, which are antimitotic agents that inhibit microtubules, and capecitabine used especially in triple-negative breast cancer can be counted. The possible drug-drug interactions of these agents and the primary therapies used in the treatment of MS were investigated. In particular, ocrelizumab and sphingosine-1-phosphate (SIP) receptor modulators have been used recently with cytotoxic chemotherapeutics such as adriamycin, cyclophosphamide, and paclitaxel, which may increase the risk of possible drug interaction with additive immunosuppressive effect.[10-12] However, there is no data on this subject. Increased

immunosuppression may cause additional comorbidities, especially infection risk, which may adversely affect MS and cancer treatment.

No drug interaction was reported between MS treatments and chemotherapy agents in any of the 17 patients screened within the study's scope and 10 patients whose follow-up data could be accessed. Due to the small number of patients in this research and the need for more data in the literature on the interactions of chemotherapeutics and treatments used in MS, further studies are needed on this subject.

CONCLUSION

This study, conducted with a limited number of patients, found no evidence of drug-drug interactions between drugs used in treating MS and antineoplastic agents. More comprehensive studies are needed on this subject.

ETHICAL APPROVAL:
Ethical approval of this study was obtained from the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Training Hospital prior to the initiation of the research work.

PATIENTS' CONSENT:
Not applicable due to the retrospective design of the study.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AT: Conception, literature review, and writing-editing.
CK: Conception, supervision, and critical review.
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