Original Article

Consolidation with Autologous Stem Cell Transplantation in Patients with Primary Central Nervous System Lymphoma

Primer Santral Sinir Sistem Lenfomalarında Otolog Kök Hücre Nakli ile Konsolidasyon Sonuçları

Bahar Uncu Ulu, Derya Şahin, Tuğçe Nur Yiğenoğlu, Tahir Darçın, Mehmet Bakırtaş, Semih Başcı, Jale Yıldız, Dicle İskender, Nuran Ahu Baysal, Merih Kızıl Çakar, Mehmet Sinan Dal, Fevzi Altuntaş

University of Health Sciences, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Department of Hematology and Bone Marrow Transplantation Center, Ankara, Turkey.

ABSTRACT

Introduction: Primary central nervous system lymphomas (PCNSL) are defined as a rare extranodal Non-Hodgkin lymphoma subgroup. The induction regimens involve high dose methotrexate-based chemotherapies mostly for the patients with PCNSL. There is still no standard approach for consolidation therapy. Recently, consolidation with autologous stem cell transplantation (ASCT) after high-dose chemotherapy has been widely used in the treatment of PCNSL. We aim to evaluate the results of PCNS patients who underwent ASCT in our center.

Methods: The data of PCNSL patients diagnosed in Hematology Unit of Dr. Abdurrahman Yurtaslan Ankara Oncology Hospital between 2010 and 2021 were analyzed retrospectively.

Results: Eleven patients were diagnosed with PCNSL diagnosis. The patients' median age included in the study was 53.5 years (range 38-68). Eight patients underwent ASCT for upfront consolidation. Seven patients achieved CR three months after ASCT; one patient was not evaluated due to exitus in the first month of the transplant. Three patients could not achieve ASCT due to transplantation ineligibility patients and mobilization failure. The median follow-up period in the study was 26 months (range 8-82 months). The median overall survival was not reached. Transplant-related mortality was 12.5%, and the mortality rate was 27% in the whole cohort. In patients who received ASCT, of the 62.5% had an almost two-year survival advantage. For the whole cohort, 73% of the patients had change for more prolonged survival among follow-up.

Discussion and conclusion: In our cohort, the PCNSL patients had mostly high-risk disease; however, three-quarters of the patients could receive ASCT, and at the same rate of the patients had advantages for long-term survival.

Keywords: Primary central nervous system lymphoma, consolidation, autologous stem cell transplantation

ÖZET

Giriş ve Amaç: Primer santral sinir sistemi lenfomaları (PSSSL) nadir görülen bir ekstranodal Non-Hodgkin lenfoma alt grubu olarak tanımlanmaktadır. İndüksiyon tedavileri, çoğunlukla PSSSL'li hastalar için yüksek doz metotreksat bazlı kemoterapileri içerir. Konsolidasyon tedavisi için hala standart bir yaklaşım yoktur. Son zamanlarda, yüksek doz kemoterapi sonrası otolog kök hücre transplantasyonu (OKHN) ile konsolidasyon tedavide yaygın olarak kullanılmaktadır. Bu çalışmada, merkezimizde OKHN uygulanan PSSSL hastalarının sonuçlarını değerlendirmeyi hedefliyoruz.

Yöntem ve Gereçler: Dr. Abdurrahman Yurtaslan Ankara Onkoloji Hastanesi Hematoloji Ünitesi'nde 2010-2021 yılları arasında tanı konulan PSSSL hastalarının verileri geriye dönük olarak incelendi.

Bulgular: On bir hastaya PSSSL tanısı konuldu. Çalışmaya dahil edilen hastaların medyan yaşı 53.5 yıl (38-68) idi. Sekiz hastaya indüksiyon tedavisi sonrası upfront konsolidasyon amacıyla OKHN uygulandı. Yedi hasta OKHN'den üç ay sonra tam yanıta ulaştı; bir hasta naklin ilk ayında çıkış nedeniyle değerlendirilmedi. Üç hastaya, transplantasyona uygun olmamaları ve mobilizasyon

First Received: 12.02.2021, Accepted: 13.04.2021 doi: 10.5505/aot.2021.09821

başarısızlığı nedeniyle OKHN yapılamadı. Çalışmadaki ortanca takip süresi 26 aydı (8-82 ay). Median genel sağkalıma ulaşılmadı. Nakille ilişkili mortalite %12.5 ve tüm kohortta mortalite oranı % 27 idi. OKHN olmuş hastaların %62.5'unda iki yıla yakın toplam sağkalım avantajı saptandı. Tüm kohort için hastaların %73'ü takipte daha uzun süreli sağkalım şansı sağlamıştır.

Tartışma ve sonuç: Bizim kohortumuzda, PSSSL hastaları çoğunlukla yüksek riskli hastalığa sahip olmasına rağmen hastaların dörtte üçü OKHN olabildi ve aynı oranda hasta uzun süreli sağkalım avantajı sağladı.

Anahtar Kelimeler: Primer santral sinir sistemi lenfoması, konsolidasyon, otolog kök hücre nakli

Introduction

Primary central nervous system lymphomas (PCNSL) are defined as a rare extranodal Non-Hodgkin lymphoma (NHL) subgroup that is typically localized to the brain, eye, spinal cord, and cerebrospinal fluid (CSF) without a primary tumor in the body [1-3]. Primary central nervous system lymphomas constitute 4% of all brain tumors and 4-6% of extranodal lymphomas [2]. The annual overall incidence rate of PCNSL is up to 0.5 cases per 100,000 [4]. Among immunocompetent individuals, the median age at diagnosis is 60 years[2]. Approximately 90-95% of PCNSL is Diffuse Large B Cell Lymphoma (DLBCL) [2]. The initial presentation usually has an intracranial mass and associated headache, confusion, weakness, and neurological deficits. Tumor infiltration can be observed in the following percentages: brain hemispheres 38%, thalamus 16%, basal ganglion 14%, corpus callosum 14%, periventricular area 12%, cerebellum 12.5%, meninges 20%, cranial nerves 16%, and spinal nerves 1% [5]. Meningeal involvement can be detected by cytological examination of CSF in 16% of the cases with PCNSL. Isolated leptomeningeal involvement is observed in less than 5% of PCNSL cases [4]. Spinal cord lymphoma is the rarest form of PCNSL and has an inferior prognosis [4,6,7]. In patients with PCNSL, various prognostic scoring systems are used to predict prognosis. The International Extranodal Lymphoma Study Group (IELSG) prognostic scoring is the most widely used one. It is based on age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), lactate dehydrogenase (LDH) level, CSF protein concentration, and involvement of the deep brain structures [8]. Scores 0-1 represents low risk, 2-3 represents intermediate risk, whereas score 4-5 represents high risk [9]. According to the IELSG scoring system, the PCNSL patients with at least two negative factors (IELSG score ≥2) showed poor survival [9]. The survival is similar to those who did not achieve complete response (CR) after two induction chemotherapy [9,10]. Therefore, a more effective treatment strategy is required, especially for PCNSL patients with an IELSG score of ≥2, or whom can not be achieved CR1 after two induction chemotherapy [8-10]. The standard treatment approach of PCNSL consists of induction and consolidation. The PCNSL is sensitive to both chemotherapy and radiotherapy. High-dose methotrexate (HDMTX)-based chemotherapy can cross the blood-brain barrier, an essential part of the treatment. Nevertheless, whole-brain radiotherapy (WBRT) as the sole therapy has been associated with poor survival and an increased risk of treatment-related neurotoxicity [10,11]. For most patients with PCNSL, the induction involves HDMTX-based chemotherapies mostly. However, there is still no standard approach for consolidation therapy. In recent years, regardless of the patients' initial prognostic scores, consolidation with autologous stem cell transplantation (ASCT) after high-dose chemotherapy has been widely used in the treatment of PCNSL [12-14]. The efficacy of upfront ASCT in PCNSL is not clearly defined due to the limited number of studies and a limited number of patients enrolled in these studies [15]. For this reason, we aim to evaluate the

results of PNSCL patients who underwent ASCT in our center.

Methods

The data of PCNSL patients diagnosed in Hematology Unit of Dr. Abdurrahman Yurtaslan Ankara Oncology Hospital between 2010 and 2021 were analyzed retrospectively. Primary central nervous system lymphoma was defined as histologically confirmed NHL restricted to the CNS, including the brain parenchyma, spinal cord, eyes, cranial nerves, or menings [16]. Diagnosis of PCNSL was histologically confirmed by stereotactic brain biopsy, surgical resection, or CSF cytology in all patients. All patients underwent pre-evaluation with contrast-enhanced brain magnetic resonance imaging (MRI), positron emission tomography to exclude systemic NHL, unilateral bone marrow aspiration and biopsy, and lumbar puncture for CSF analysis unless contraindicated. High CSF protein concentration was defined as more than 0.45 g/l in patients younger than 60 years old and more than 0.6 g /l in patients at the age of 60 and older[8]. Involvement of deep brain structures was defined as involvement of periventricular regions, basal ganglia, brain stem, and cerebellum. At the time of diagnosis, IELSG scoring (age> 60 years, ECOG PS ≥2, high LDH, high CSF protein concentration, and deep brain structures involvement) was performed in all patients [8,10]. Response to induction chemotherapy was evaluated by comparing brain MRI performed before and after the second induction course and after the induction regimen. Response to treatment was assessed according to the criteria of the International PCNSL Collaborative Group [17]. Patients with a chemosensitive response to induction therapy underwent upfront ASCT consolidation. Patients who had chemo-refractory response received a salvage regimen. Among ASCT, the engraftment definition for neutrophil was defined as the first day when the absolute neutrophil count (ANC) was >500/mm^3 or 1000/mm^3 for three consecutive days, and thrombocyte engraftment was defined as the first day when thrombocyte count was >20000/mm^3 for three consecutive days without transfusion. All patients received weight adapted G-CSF before the neutrophil engraftment. Overall survival was calculated from the date of histological diagnosis to death or the last date of follow-up. Progression-free survival was calculated from the date of histological diagnosis to disease progress, death, or date of the latest follow-up for progression-free patients, whichever occurred first. Transplant-related mortality (TRM) was defined as death within the first 100 days after ASCT [18].

The local human research ethics committee approved this study. All procedures performed in studies involving human participants were under the national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Permission granted /Decision number: 2020-12/910).

All statistical analyses were conducted using SPSS V21.0 (SPSS Inc., Chicago, IL) software. Descriptive statistics were applied to summarize the data. The categorical data were reported as rates, and numeric data were reported as medians and average ± standard deviations. The Kruskal Wallis Test was used to analyze engraftment times between the groups. Kaplan Meier test was used to analyze PFS and OS

Results

Eleven patients were diagnosed with PCNSL diagnosis at our center. The patients' median age included in the study was 53.5 years (range 38-68 years). The male to female ratio was 4.5. All patients' disease stage was

Table 1: Patients' characteristics

Patients	N (number)
Age (median)	53.5 (38-68)
Gender (Female /Male)	2/9
DLBCL Histological Subtype	
Germinal center B cell	4
Activated B cell	5
Other	1
Unknown	1
Induction regimen	
R-HyperCVAD	4
MATRIX	4
MTX-Ara-C	2
R-CHOP	1
ASCT	
Received	8
Not Received	3
ASCT conditioning	
TECA	5
Thiotepa- carmustine	3
Radiotherapy	
Received	6
Not received	5
The quantity of infused $CD34^+$ Stem Cells (median)	10.06 $x10^6$ /kg (4.1-16)

DLBCL: Diffuse Large B cell Lymphoma; R-HyperCVAD course A: cyclophosphamide, vincristine, doxorubicin, dexamethasone, and rituximab; Course B, methotrexate, cytarabine, and rituximab; MATRIX: High dose methotrexate, high dose cytarabine, thiotepa, and rituximab; MTX-Ara-C: methotrexate, cytarabine; R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ASCT: autologous stem cell transplantation; TECA: thiotepa, etoposide, and carboplatine

localized to the central nervous system; two had bulky disease. All of the patients had Diffuse Large B cell Lymphoma (DLBCL) histological subtype of NHL. Four patients had germinal center B cell-like, five patients had activated B cell-like, one patient had T-cell and histiocyte-rich type DLBCL, and one patient's immunohistochemical subtype was not determined. The patients' clinical features are shown in Table 1.

The IELSG score was low risk in three patient; the score was ≥ 2 in eight patients that means intermediate and high risk. One patient with an IELSG score of 1 died due to sepsis in the first month of the transplant. As the induction regimen, R-HyperCVAD (the drugs used in course A: cyclophosphamide, vincristine, doxorubicin, dexamethasone, and rituximab; Course B consists of methotrexate, cytarabine, and rituximab) was given to four patients, methotrexate cytarabine to two patients, MATRIX (HDMTX, high dose cytarabine, thiotepa, and rituximab) to four patient, and R-CHOP (rituximab, cyclo-phosphamide, doxorubicin, vincristine, and prednisone) to one patient.

Seven patients achieved CR1 after induction therapy. One patient received methotrexate cytarabine, and one patient who received R-CHOP had stable disease after first-line induction, so they had hyperCVAD for salvage and achieved CR2. Of the two patients who had MATRIX for induction had refractory disease, they had RT and temozolomide for salvage.

Six patients received radiotherapy among follow-up, of the three patients received radiotherapy after upfront ASCT. Six patients received a median of four intrathecal chemo-therapy during the induction regimen.

Eight patients underwent upfront ASCT. The TECA (thiotepa, etoposide, and carboplatine) regimen was used as the conditioning regimen in five patients, and the thiotepa-carmustine regimen was used in three patients. Median neutrophil engraftment duration was 12 (range 8-16) days, and median platelet engraftment was 12 (range 9-14) days.

Seven patients achieved CR three months after ASCT; one patient was not evaluated due to exitus in the first month of the transplant. Three patients could not achieve ASCT due to transplantation ineligibility (n:2) patients and mobilization failure (n:1). Who did not received ASCT, one of them had temozolomide for consolidation, two of them had temozolomide for salvage.

The median follow-up period in the study was 26 months (range 8 month-82 months). The median follow-up time after ASCT was 20 months (range 1-63 months).

The median overall survival was not reached. Transplant-related mortality was 12.5%, and the mortality rate was 27% in the whole cohort. Three patients died in the first year of the ASCT due to infection. In patients who received ASCT, the median survival time from diagnosis was 29 months (range 8-82 months), and 62.5% of patients had an almost two-year survival advantage. For the whole cohort, 73% of the patients had change for more prolonged survival among follow-up.

Discussion

Primary central nervous system lymphomas are rare and aggressive malignancies. Besides low incidence, the data are limited about standard induction and consolidation treatment. We aim to evaluate the outcome of the PCNL patients' who received ASCT. In our cohort, IELSG score was ≥2 of 72% of patients and had mostly high-risk disease. However, 73% of the patients could receive ASCT, and at the same rate of the patients had long-time survival.

The two-year OS is 80% in patients with an IELSG score of 0-1 points, 48% in those with 2-3 points, and 15% in those with 4-5 points [8]. As the expected 2-year OS is less than 50% in patients with an IELSG score of 2 at the time of diagnosis, intensive treatments are required, especially for this high-risk group of patients. Furthermore, failure to achieve CR after HDMTX-based induction chemotherapy is associated with poor survival, requiring a more effective treatment strategy for these patients [10,19]. Consolidation with WBRT or ASCT should be considered, especially in high-risk patients, due to the low response rates of standard HDMTX-based induction chemotherapy alone [8,20]. In a recent randomized phase III study, no survival advantage was detected when WBRT was used as consolidation treatment [19]. Additionally, WBRT has been associated with neurotoxicity and a high relapse rate [21]. WBRT should be considered in refractory patients or patients who cannot tolerate high-dose chemotherapy. In our cohort, nearly half of the patients had WBRT for palliation or salvage regimen. We preferred ASCT initially for consolidation instead of WBRT to avoid neurotoxicity.

Since ASCT was first used in relapsed PCNSL in 1996, most centers have been used as consolidation treatment in patients with PCNSL [22]. In a multicenter phase II study, 23 PCNSL patients younger than 65 years received HDMTX based induction followed by ASCT with carmustine-thiotepa conditioning regimen. Twenty-one patients received WBRT (45 Gy, two doses of 1 Gy/d) for consolidation after ASCT. With a median follow-up of 63 months, 5-year estimated OS was 87%, and the 5-year probability of relapse-related death was 8.7% [23]. In another study, 13 patients with PCNSL received HDMTX based induction followed by ASCT with carmustine-thiotepa conditioning regimen. Radiotherapy was restricted to patients who did not achieve CR. With a median follow-up of 25 months, 3-year disease-free survival (DFS), and OS was 77% [24]. In a review, 2-year PFS was 69% (range 54% -81%) and 2-year OS was 84% (range 83%-91%) and TRM was 3% for PCNSL patients undergoing upfront ASCT following regimens containing thiotepa and / or WBRT. In the same review, 2-year PFS was 44% (range 25% -62%), 2-year OS was 65% (range 60% -70%), and TRM was 4% in patients who underwent upfront ASCT following thiotepa-free regimens. Thiotepa containing regimens were found to be associated with better PFS and OS when compared to thiotepa-free regimens. Addition of WBRT has not been shown to affect OS [15]. In the study conducted by Cho et al., 2-year OS was 93.3%

in patients who underwent upfront ASCT and 72.9% in patients who underwent ASCT after salvage therapy, but this difference did not achieve statistical significance. However, PFS was significantly higher in patients consolidated with upfront ASCT than those who underwent ASCT after salvage therapy (91.7% and 25.0%, respectively; P = 0.001) [25]. In our center, if the patient were eligible for ASCT, patients were performed upfront ASCT instead of waiting for relapse. We observed that 62.5% of the PCNSL patients who underwent upfront ASCT could survive among follow-up. The median durations for neutrophil and platelet engraftment were ten days (9–13 days) and 14 days (11–24 days) in the same study during ASCT [22]. We administered thiotepa based conditioning mostly, and the median neutrophil and platelet engraftment duration was 12 days in our study.

We administered HDMTX based induction regimens, and we preferred ASCT consolidation for transplantation eligible patients mostly. However, IELSG score mostly intermediate and high risk in our cohort, 73% of the patients had change for long time survival among follow-up. One of our limitations was the number of the cohort, and it was lower due to the low incidence of PCNSL. The other limitation was the retrospective design of our study.

In conclusion, PCNSL is a rare subtype of NHL and DLBCL is the most seen NHL subtype. There is no standard induction treatment nor consolidation, or conditioning regimen. Therefore, bone marrow transplantation centers need to report PCNSL patients' outcomes to contribute to the literature to determine the optimum induction treatment, consolidation, or conditioning regimen.

REFERENCES

1-Bayındır Ç, Balak N, Mete Ö, et al. Primer Santral Sinir Sistemi Lenfomaları:91 hastanın klinikopatolojik retrospektif analizi. Turkiye Klinikleri J Surg Med Sci. 2007; 3(34): 175-81

2-Roth P, Korfel A, Martus P, Weller M. Pathogenesis and management of primary CNS lymphoma. Expert Rev Anticancer Ther 2012; 12: 623-633.

3-Grommes C, DeAngelis L.M. Primary CNS Lymphoma. J Clin Oncol. 2017; 35(21): 2410-2418.

4-Villano JL, Koshy M, Shaikh H, et al. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer. 2011; 105(9): 1414-8. 5

5- Kuker W, Nagele T, Korfel A, et al. Primary central nervous system lymphomas (PCNSL): MRI features at presentation in 100 patients. J Neurooncol 2005; 72: 169–77.

6-Ferreri AJ, Reni M, Pasini F, et al. A multicenter study of treatment of primary CNS lymphoma. Neurology 2002; 58: 1513-1520.

7-Bromberg JE, Siemers MD, Taphoorn MJ. Is a "vanishing tumor" always a lymphoma? Neurology 2002; 59: 762-764.

8-Ferreri, A.J., Blay, J.Y., Reni, M., et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. Journal of Clinical Oncology, 2003; 21, 266–272.

9-Ferreri AJ, Marturano E. Primary CNS lymphoma. Best Pract Res Clin Haematol 2012; 25: 119-130.

10-Pels, H., Juergens, A., Schirgens, I., et al. Early complete response during chemotherapy predicts favorable outcome in patients with primary CNS lymphoma. NeuroOncology, 2010; 12, 720–724.

11-Nelson, D.F., Martz, K.L., Bonner, H., et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. International Journal of Radiation Oncology Biology Physics, 1992; 23, 9–17.

12-Omuro, A., Correa, D.D., DeAngelis, L.M., et al. RMPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. Blood, 2015; 125: 1403–1410.

13-Schorb, E., Kasenda, B., Atta, J., Kaun, S., et al. Prognosis of patients with primary central nervous system lymphoma after high-dose chemotherapy followed by autologous stem cell transplantation. Haematologica, 2013; 98: 765–770.

14-Soussain, C., Hoang-Xuan, K., Taillandier, L., et al. Intensive chemotherapy followed by hematopoietic

stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Societe Francaise de Greffe de Moelle Osseuse-Therapie Cellulaire. Journal of Clinical Oncology, 2008; 26: 2512–2518.
15-Kerbauy M, Moraes F, Kerbauy L, et al. Autologous Stem Cell Transplantation (ASCT) As Upfront Treatment in Primary Central Nervous System Lymphoma (PCNSL): A Systematic Review and Comparative Analysis in Clinical Trials Setting. Blood 2016; 128: 2272
16-Deckert, M., Engert, A., Bruck, W., et al. Modern concepts in the biology, diagnosis, differential diagnosis and treatment of primary central nervous system lymphoma. Leukemia, 2011; 25: 1797–1807.
17-Abrey L.E., Batchelor TT, Ferreri AJM, Gospodarowicz M, Pulczynski EJ, Smith EZR, et al. Report of an International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma. Journal of Clinical Oncology 2005; 23; 5034-5043.
18-Davies SM, Kollman C, Anasetti C et al. Engraftment and survival after unrelated-donor bone marrow transplantation: a report from the national marrow donor program Blood 2000; 96: 4096 4102
19- Korfel A, Thiel E, Martus P, et al. Randomized phase III study of whole-brain radiotherapy for primary CNS lymphoma. Neurology 2015; 84: 1242– 1248.
20-Abrey LE, Ben-Porat L, Panageas, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. Journal of Clinical Oncology 2006; 24: 5711–5715
21- DeAngelis LM, Seiferheld W, Schold SC, et al. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93- 10. Journal of Clinical Oncology 2002; 20: 4643–4648.
22-Khalfallah S, Stamatoullas A, Fruchart C, et al. Durable remission of a relapsing primary central nervous system lymphoma after autologous bone marrow transplantation. Bone Marrow Transplantation 1996; 18: 1021–1023.
23- Illerhaus G, Marks R, Ihorst G, et al. Highdose chemotherapy with autologous stem-cell transplantation and hyperfractionated radiotherapy as first-line treatment of primary CNS lymphoma. Journal of Clinical Oncology 2006; 24: 3865– 3870.
24- Illerhaus G, Muller F, Feuerhake F, Schafer AO, Ostertag C. & Finke J. High-dose chemotherapy and autologous stem-cell transplantation without consolidating radiotherapy as first-line treatment for primary lymphoma of the central nervous system. Haematologica 2008; 93: 147–148.
25-Cho H,Chang J, Kim Y, et al. The role of upfront autologous stem cell transplantation in high-risk younger patients with primary central nervous system lymphoma. British Journal of Haematology, 2016; 174: 444–453.

Corresponding author e-mail: baharuncu@gmail.com

Orcid ID:
Bahar Uncu Ulu 0000-0002-6230-9519
Derya Şahin 0000-0002-0945-8398
Tuğçe Nur Yiğenoğlu 0000-0001-9962-8882
Tahir Darçın 0000-0001-5073-1790
Mehmet Bakırtaş 0000-0003-3216-482X
Semih Başçı 0000-0003-4304-9245
Jale Yıldız 0000-0002-8235-1570
Dicle İskender 0000-0002-6062-6422
Nuran Ahu Baysal 0000-0002-2425-3374
Merih Kızıl Çakar 0000-0003-0978-0923
Mehmet Sinan Dal 0000-0002-5994-2735
Fevzi Altuntaş 0000-0001-6872-3780

Doi: 10.5505/aot.2021.09821

