

Cranial Involvement in a Follicular Lymphoma Patient with Systemic Complete Remission After Yttrium-90-Ibritumomab-Tiuxetan Treatment: Scientific Letter

Yttrium-90-Ibritumomab-Tiuxetan Tedavisi Sonrası Sistemik Tam Remisyon Gelişen Foliküler Lenfoma Olgusunda İzole Beyin Nüksü

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ABSTRACT Non-Hodgkin's lymphoma is a heterogeneous group of lymphoproliferative disorders with varying patterns of behavior and treatment responses. Advances in understanding of tumor biology have made it possible to exploit novel treatment strategies such as monoclonal antibodies and their conjugation with radioimmunotherapy was recommended in patients with first relapse of low-grade lymphomas such as follicular lymphoma after rituximab containing chemotherapy. Treatment with radioimmunotherapy such as yttrium-90-ibritumomab-tiuxetan utilizes a monoclonal anti-CD20 antibody to deliver beta-emitting yttrium-90 to the malignant B-cells. Clinical trials have demonstrated its efficacy, which is largely independent of the intrinsic activity of the anti-CD20 antibody. Relapses of nodal lymphomas usually occur in extra lymphoid areas. Central nervous system (CNS) involvement develops in less than 1% of patients with lymphomas. Herein, we are presenting a rare case of CNS involvement of follicular lymphoma in a patient who has achieved systemic complete remission after yttrium-90-ibritumomab treatment.

Key Words: Lymphoma; lymphoma, follicular

ÖZET Non-Hodgkin lenfoma (NHL) değişik davranış ve tedavi yanıtı bulunan heterojen bir lenfoproliferatif hastalık grubudur. NHL tümör biyolojisinin son yıllarda daha iyi anlaşılması ile hedef tedaviler ve radyoimmünodetavi (RİT) gibi yeni tedavi seçenekleri geliştirilmiştir. RİT düşük dereceli lenfomalarda rituximab tedavisi sonrası nüks eden olgularda önerilmektedir. RİT tedavi seçeneklerinden yttrium-90-ibritumomab, rituximab yardımı ile CD20 (+) lenfositlere tutunarak çevredeki lenfositlere radyoaktif bir madde olan yttrium-90'nın iletilmesini sağlar. Klinik çalışmalar RİT'in rituximab'dan bağımsız olarak etkinliğini göstermiştir. Nodal lenfomalarda ekstranodal tutulum sık olarak görülmektedir ancak santral sinir sistemi tutulumları arasında beyin tutulumu %1'in altındadır. Biz burada yttrium-90-ibritumomab ile tedavi edilip tam remisyon sağlandıktan sonra sistemik hastalık halen tam remisyonunda iken izole santral sinir sistemi nüksü gelişen foliküler lenfoma olgumuzu sunduk.

Anahtar Kelimeler: Lenfoma; foliküler lenfoma

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Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of lymphoproliferative disorders with varying patterns of behavior and treatment responses.¹ Advances in our understanding of tumor biology have made it possible to exploit novel treatment strategies such as monoclonal antibodies, and their conjugation with radioimmunotherapy (RIT) was recommended in patients with first relapse of low-grade lymphomas such as follicular lymphoma after rituximab-containing chemotherapy. Relapses of nodal lymphomas usually occur in extralymphoid areas.

CNS involvement develops in less than 1% of patients with lymphomas.² Herein, we are presenting a rare case report of CNS involvement in a follicular lymphoma patient with systemic complete remission after yttrium-90-ibritumomab-tiuxetan treatment.

A 52-year-old male patient was admitted in our clinic in March 2003 with a history of fatigue, night sweats, fever, and left supraclavicular masses. On physical examination, 3 cm left supraclavicular and 4 cm bilateral axillary and inguinal lymphadenopathies were detected. After excisional biopsy of the supraclavicular mass, histopathologic examination revealed high-grade, diffuse B cell CD 20 (+) lymphoma. Performance status was ECOG 1 prior to the administration of systemic chemotherapy. Results of initial biochemical analyses were as follows: LDH: 1135 U/L (100-190 U/L), erythrocyte sedimentation rate (ESR) 80 mm/hour, liver function tests and bilirubine levels were normal. There were multiple supraclavicular, bilateral axillary, mediastinal, and abdominal lymphadenopathies detected on thoraco-abdominal computerized tomography. The disease was stage IV according to the Ann Arbor staging system. International prognostic index score showed low intermediate risk. He had been treated with six cycles of R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) after which he responded partially. Then, he was treated with the R-DHAP (Rituximab, Cisplatin, Cytarabine, Dexamethasone) regimen and did not respond to this protocol after his previous partial response. A second excisional biopsy was performed from another lymphoid area, ie. right axillary mass. Immunohistopathological examination revealed follicular lymphoma, CD 20(+), and bcl-2 (+). Yttrium-90-ibritumomab-tiuxetan was administered for residual low-grade disease. After two months of yttrium-90-ibritumomab-tiuxetan therapy, ESR was 12 mm/hour and no lymphadenopathies were detected on physical examination and on thoraco-abdominal computerized tomography. He had complete remission of the disease. After two years of complete remission, he presented with 3 weeks of emesis, progressive headache and

depression symptoms. Cranial MRI scan revealed two masses with 3 cm and 4 cm diameters in the subcortical white matter of the frontal lobe of the brain with diffuse homogeneous contrast with irregular borders and without surrounding edema, ring enhancing lesion and necrosis. Lumbar tap did not reveal any malignant cells in the cerebrospinal fluid. Stereotactic biopsy was considered but the lesions were not in an appropriate localization for biopsy. High dose methotrexate was suggested but was refused by the patient. Thus, palliative whole-brain radiotherapy was applied, which resulted with complete response.

Follicular lymphomas are among the group of indolent lymphomas. About 80% of patients with indolent B-cell NHLs are in the advanced stage of disease and have no curative treatment option. Additionally, the median survival ranges between 8-10 years.³ CD20-directed monoclonal antibodies clearly demonstrate clinical efficacy in patients with B cell indolent NHL. Rituximab activity can be quite meaningful, and is associated with manageable toxicity, but unfortunately substantial numbers of patients do not respond and many relapse. These cases of refractory and relapsed low-grade follicular or transformed NHL, including those with rituximab refractory disease can be effectively treated with RIT. Yttrium-90-ibritumomab-tiuxetan was the first RIT to be approved for use in malignant disease.⁴ Recently, yttrium-90-ibritumomab-tiuxetan was shown to be effective in these refractory patients. Wiseman and Witzing reported long-term responses in a retrospective study of 211 patients with relapsed or refractory low-grade lymphoma.⁵ These patients who were treated with yttrium-90-ibritumomab-tiuxetan had a median time to disease progression (TTP) of 29.3 months. Although our patient had a 26-month TTP similar to the results of Wiseman and Witzing, he had a relapse with cranial metastasis without any other systemic disease. CNS involvement of lymphoma should be distinguished from other brain metastases such as solid tumors, and primary CNS lymphoma. Stereotactic biopsy and immunohistopathological examination should be made for diagnosis, although radiological findings

will be helpful for the diagnosis of brain masses that are not appropriate for stereotactic biopsy such as in our patient.²

Standard doses of systemic chemotherapeutics, targeted therapies such as rituximab and RITs do not cross the blood-brain barrier sufficiently to treat CNS involvement of lymphoma and primary CNS lymphomas are treated with high dose systemic chemotherapy, intrathecal chemotherapy for meningeal metastases and rarely surgery for patients acutely deteriorating due to herniation from a large tumor mass.² Nonetheless, after

two years of yttrium-90-ibritumomab-tiuxetan administration, our patient had brain involvement without other systemic disease.

In conclusion, we wanted to remind physicians that refractory or relapsed low-grade follicular or transformed NHL patients who responded completely to treatment with yttrium-90-ibritumomab-tiuxetan should be followed-up for primary cranial relapse without systemic disease. The patients who had complete response to targeted therapies such as rituximab and RITs will be evaluated by prophylactic cranial therapies.

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