Failure of yttrium-90 (^{90}Y)-ibritumomab tiuxetan radioimmunotherapy (Zevalin®) with fatal side effects in relapsed/refractory diffuse large B-cell NHL transformed from other lymphomas

Diğer lenfomalardan transforme olmuş relaps/refrakter difüz büyük B hücreli lenfomada ölümcül yan etkisi ile yttrium-90(^{90}Y)-ibritumomab tiuxetan radyoimmunoterapi (Zevalin®)`nin başarısızlığı

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The non-Hodgkin's lymphomas (NHL) constitute a diverse group of lymphoid malignancies ranging from indolent to highly aggressive clinical behavior and they can transform to each other [1]. The inherent radiosensitivity of most NHLs and the availability of a good antigenic target (CD20) and corresponding monoclonal antibody provided the rationale for the development of radioimmunotherapy (RIT) for the treatment of B-cell NHL [2]. RIT is a novel treatment modality that combines the benefits of radiotherapy and immunotherapy, enabling multiple sites of disseminated disease to be treated simultaneously and effectively, while minimizing toxicity to normal tissues [3]. Yttrium-90 (^{90}Y)-ibritumomab tiuxetan RIT (Zevalin®) has been registered as an effective treatment for follicular NHL [4]. However, little is known about its efficacy and safety in diffuse large B-cell lymphoma (DLBCL). We administered Zevalin® to two patients with relapsed or refractory DLBCL in the context of 'off-label indication'. We herein report the fatal side effects and inefficiency of Zevalin® in these two patients with DLBCL transformed from other lymphoid malignancies.

A 51-year-old male patient was initially diagnosed with stage III-B follicular lymphoma three years before. At the first assessment, there was no bone marrow involvement. A computed tomography (CT) scan of the abdomen revealed hepatosplenomegaly and bulky intraabdominal lymph nodes (7x5cm). After eight cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy, complete remission (CR) was achieved. Four months later, while off-therapy, disease progression was noted without bone marrow involvement. Two cycles of R-ICE (rituximab, ifosfamide, carboplatin, etoposide) salvage chemotherapy was performed. CT scan of the abdomen and thorax showed no improvement in lymph nodes after chemotherapy. Hence, the patient's disease was accepted as chemo-resistant. Rituximab 250 mg/m^2 was given as an intravenous infusion on days 1 and 8. ^{90}Y-ibritumomab tiuxetan was administered within 4 hours of the predose of rituximab on day 8 by a 10-minute intravenous 'slow push' at a dose of 0.4 mCi/kg. Two months after ^{90}Y-ibritumomab tiuxetan therapy, transformation to diffuse large B cell NHL occurred. ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) chemotherapy was given but the patient died soon after chemotherapy with no disease response due to sepsis following disseminated intravascular coagulation and intracranial bleeding.

The second patient was a 23-year-old male initially diagnosed as stage III nodular sclerosing type Hodgkin disease in December 2004. He had massive hepatosplenomegaly and widespread enlarged lymph nodes with a mediastinal bulky dis-

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ease (8x8cm). Gallium scintigraphy was also positive for adrenal involvement. After two cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy, progression was observed. New lesions in the liver and pancreas were detected by computed tomography. Involved field radiotherapy was given to the mediastinum. Low molecular weight heparin was also started because of vena cava superior syndrome. In May 2005, intestinal obstruction and perforation developed and ileal resection biopsy revealed a new pathological entity, diffuse large B-cell NHL. After eight cycles of R-CHOP-14 chemotherapy, a partial remission was achieved but unfortunately central nervous system relapse developed with an intracranial mass (6.4x2.7 cm). After one cycle of high-dose methotrexate and cytosine arabinoside chemotherapy, he received radiotherapy to the mediastina. Progression of mediastinal lymph nodes occurred under R-ICE chemotherapy, while in the fourth cycle. He had no HLA identical sibling donor, so rituximab and ^{90}Y-ibritumomab were administered as in the previous patient. However, disease progression occurred and the patient died after three weeks.

DLBCL is the second most common histology of all lymphomas, and although considered aggressive in nature, it can be treated with curative intent with standard immunochemotherapy [1]. In contrast, patients with follicular and other indolent lymphomas can sustain prolonged remission periods, but eventually relapse and require subsequent courses of therapy that lead to fewer and shorter remissions [2]. ^{90}Y-ibritumomab tiuxetan RIT is a new and effective treatment for relapsed or refractory B-cell NHL. This first-in-class RIT combines the cell-specific targeting power of the anti-CD20 monoclonal antibody with the tumor cell-killing ability of 90Y radiation [4]. Whereas total body irradiation (TBI) delivers an equivalent dose of radiation to all organs, radioimmunoconjugates specific for tumor-associated antigens such as CD20 deliver a 10-fold or greater radiation dose to the tumor than to the whole body [5]. The phase I trials demonstrated that in patients with a platelet count of greater than or equal to 150x10^9/L, a schedule of intravenous rituximab 250 mg/m^2 on days 1 and 8, and 0.4 mCi/kg of intravenous ^{90}Y-ibritumomab tiuxetan on day 8 was safe and efficacious and did not require stem cells [6]. Rituximab is given to enable clearance of peripheral B-cells and to maximize biodistribution prior to radioimmunoconjugate therapy [7]. Although high response rates have been suggested in the literature, our two relapsed and refractory NHL patients showed no benefit from the RIT approach. The first patient exhibited fatal septic side effects, while the second was lost with disease progression. Therefore, Zevalin® even precipitated the poor outcome of these unique transformed lymphoid malignancies. Elucidation of these adverse observations with controlled clinical trials could lead to the identification of RIT for the clinical management of lymphoid malignancies with such a unique changing clinicopathological disease course.

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