Original Study

Patients Older Than 65 Years With Non-Hodgkin Lymphoma Are Suitable for Treatment With ^{90}Yttrium-Ibritumumab Tiuxetan: A Single-Institution Experience

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Abstract

Radioimmunotherapy in B-cell malignances is currently recommended as consolidation and salvage therapy, depending on the lymphoma subtype. However, the major clinical trials have included mostly young patients, in contrast to common practice. We analyzed our single-center experience with 108 patients, 40% of them aged > 65 years, according to differences in age, tolerability, and efficacy.

Background: The mean age of patients included in clinical trials does not reflect the current clinical practice for patients with B-cell non-Hodgkin lymphoma (B-NHL). We compared our outcomes for patients with B-NHL aged < 65 and > 65 years who were treated with 90-yttrium-ibritumomab tiuxetan therapy (^{90}Y-IT). **Patients and Methods:** A total of 108 patients who had received ^{90}Y-IT according to the hospital protocol (ISCRTN36210045) were eligible. A quality of life (QoL) assessment using the Medical Outcomes Study short form 36-item survey was performed for patients aged > 65 years. **Results:** Of the 108 patients, 43 were aged > 65 years (mean age, 73.4 years; men 46.15%); 37 had follicular NHL (86.0%). Also, 27 patients had previously undergone < 2 therapy regimens (62.8%). The mean follow-up period was 45.2 months. The mean progression-free survival (PFS) period was 71.3 months, and the mean overall survival was 78.2 months. The median values were not reached. The overall response rate was 90.5%, and a complete response was observed in 36 of the 43 patients aged > 65 years (85.7%). Neutropenia (43.3%) and thrombocytopenia (45.2%) were the most frequent grade 3 and 4 toxicities. Five patients required a red blood cell transfusion and 11, a platelet transfusion. Five patients aged > 65 years (11.6%) developed a second tumor. These outcomes were similar to those for the younger patients. The QoL assessment showed scores similar to those of general population for general health and social functioning. **Conclusion:** This is the largest cohort of NHL treated with RIT in a single institution in Spain. We observed a high response rate and prolonged PFS in patients with B-NHL, independent of patient age. Thus, consolidation RIT offers better outcomes with manageable toxicity.

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Introduction

Non-Hodgkin lymphoma (NHL), as a group, ranks as the seventh most common cancer in the United States and represents about 4% of all malignancies.[1,2] In people aged > 60 years, the incidence will be 1 in 167 for men and 1 in 228 for women. In those aged > 70 years, the incidence increases to 1 in 57 for men and 1 in 71 for women.[3]

Follicular lymphoma (FL) is the second most frequent NHL subtype after diffuse large B-cell lymphoma and has been studied extensively, owing to its prevalence, distinctive histologic features, and relatively preserved classification schema. FL accounts for about

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22% of NHL in adults worldwide but represents 40% of all lymphomas diagnosed in the United States and Western Europe.[4] The clinical course can vary widely. Some patients will present with very aggressive disease and die within 1 year; however, the more frequent behavior has been a chronic disease characterized by recurrent relapses with prolonged survival.[5,6] Different strategies have been applied to treat FL; however, until now it has been an incurable disease. One of the most widely accepted therapeutic approaches to indolent lymphoma has been to maintain the best quality of life and to treat only when the patients require it.[7] The emergence of CD20 immunotherapy with a monoclonal antibody has been a major advance in all these lymphomas, especially in FL management. Its use has permitted patients longer periods without therapy. However, patients who develop a relapse will require another treatment regimen that will usually include other drugs and/or stem cell transplantation with serious adverse events possible. These include cardiotoxicity, peripheral neuropathy, lymphopenia, nausea, vomiting, alopecia, and so on, creating the necessity to achieve better and more durable responses.[8-10]

It is known that lymphoma cells are sensitive to radiation.[10,11] Radioimmunotherapy (RIT) combines the selectivity of anti-CD20 immunotherapy with an attached radioisotope, making it possible to deliver radiation to within the tumor. This therapy has been approved since 2002.[12,13] Increasing evidence on RIT use has revealed it to be safe and to improve progression-free survival (PFS) and overall survival (OS) in patients with FL. The First-Line Indolent Trial (FIT) proved the effectiveness of 90-yttrium-ibritumomab tiuxetan therapy (^{90}Y-IT) in the setting of relapse, resulting in additional investigation.[14] Also, ^{90}Y-IT has been approved for all relapsed B-cell CD20$^+$ lymphomas and FL as consolidation therapy. This therapy alone significantly prolonged the median PFS after a median follow-up period of 3.5 years and converted 77% of those with a partial response (PR) after induction to a complete response (CR), for a CR rate of 87%, with low associated toxicity.[15,16] The 8-year PFS rate was 48% for patients who achieved a CR.[17]

The principal clinical trials included patients with a mean age of 49 to 59 years.[15,17] However, in actual clinical practice, elderly patients will be more commonly encountered, with an average age at the diagnosis of FL of 60 to 65 years.[10] Thus, we believe it important to analyze this population. It is unclear whether NHL presents with different behaviors and responses to RIT in this population or whether elderly patients are more predisposed to developing adverse effects to RIT.

Since September 2005, ^{90}Y-IT has been available in Spain. It was first applied therapeutically only for relapsed and refractory B-cell NHL. After approval, it was included as a part of consolidation therapy after first-line immuno- or chemoimmunotherapy for patients with FL. At our institution, we have treated 43 patients aged $>$ 65 years and 65 patients aged $<$ 65 years using our routine clinical practice protocol. All the patients had met the same inclusion criteria and less subjective variations. Our experience can be of great value to improving the scientific knowledge. We present the outcomes derived from ^{90}Y-IT use in the patients aged $>$ 65 years with NHL.

Patients and Methods

We designed a clinical protocol conducted by a multidisciplinary team comprising clinical hematologists, nuclear medicine physicians, radiopharmacists, and nurses at Miguel Servet University Hospital (Zaragoza, Spain) and registered under hospital protocol ISCRTN36210045. The Ethical Committee of Clinical Research approved the study, which was performed in accordance with the current version of the Declaration of Helsinki.

We began in September 2005 and established the use of ^{90}Y-IT in patients aged $\geq$ 18 years, with an excisional biopsy-confirmed diagnosis of CD20$^+$ F-NHL grade 1, 2, or 3a, according to the revised World Health Organization (WHO) classification system, who had relapsed or refractory disease after at least first-line combined chemotherapy. In 2007, the therapeutic inclusion indication was extended to other B-cell lymphomas (in particular, indolent subtypes), diffuse large B-cell lymphomas of follicular origin, and as consolidation after first-line chemotherapy for patients with a CR or PR confirmed by positron emission tomography—computed tomography (PET-CT).

Before being considered for RIT, all patients underwent a thorough examination and had blood samples taken for a complete blood count (CBC) with leukocyte differential and platelet counts. They also underwent a PET/CT scan, bone marrow examination, and biopsy. Basic blood chemistry tests were also performed for serum creatinine, liver function tests, uric acid, and lactate dehydrogenase.

Additional inclusion criteria, applied to all patients, were Eastern Cooperative Oncology Group performance status $\leq$ 2, absolute neutrophil count $\geq$ 1,500/μL, absolute platelet count (APC) $\geq$ 100,000/μL, bone marrow total lymphocytes $\leq$ 25% by morphologic counting of all cellularity, serum bilirubin $\leq$ 2.0 mg/dL, and serum creatinine $\leq$ 2.0 mg/dL. All patients were requested to sign an informed consent form.

The therapeutic regimen administered was as follows an intravenous infusion of 250 mg/m^2 rituximab on day 1 was performed to reduce nonmalignant binding with CD20$^+$ B cells, both circulating and within the spleen. An intravenous infusion of a second dose of 250 mg/m^2 rituximab was given on day 7, followed by a weight-based dose of ^{90}Y-IT administered by a slow intravenous injection over 10 minutes within 4 hours after rituximab infusion. The ^{90}Y-IT dose was 0.4 mCi/kg for patients with a platelet count $>$ 150,000/μL and 0.3 mCi/kg for patients with a platelet count of 149,000 to 100,000/μL.

A CBC was performed weekly in all patients for the first 8 weeks after ^{90}Y-IT infusion or until the patient had recovered from grade 3 to 4 cytopenia. Hematologic toxicity was defined using the WHO criteria. The transfusion threshold was an APC $<$ 20,000/μL in outpatients and a hemoglobin level $<$ 8 g/dL or symptomatic anemia with poor tolerance. Patients with grade 4 neutropenia received a single dose of pegfilgrastim for recovery.

The response assessment was performed at 12 weeks after treatment. A PET-CT scan was performed in all cases, and the response criteria used were the same as those from the International Working Group (IWG). Subsequent follow-up evaluation also included a CBC and physical examination every 3 to 4 months during the first 2 years after ^{90}Y-IT therapy and then every 6 months until relapse or death. A second PET-CT scan was performed 1 year after therapy; subsequently, the follow-up protocol was according to routine clinical practice.