Clinical Study

RIT with $^{90}$Y-Ibritumomab Tiuxetan in Follicular Non-Hodgkin Lymphoma: Evaluation of Recent Outcomes in a Single Institution

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1. Introduction

The beginning of immunotherapy with the approval of the anti-CD20-specific monoclonal antibody (Mo-Ab) rituximab by the Food and Drug Administration (FDA) in 1997, as part of the first-line treatment of non-Hodgkin B-cell lymphoma (NHL), marked an advance in response to treatment and overall survival in the lymphoproliferative disorders. The pivotal clinical trials of follicular non-Hodgkin lymphoma (F-NHL) that compared anthracycline-based combination chemotherapy with and without rituximab showed clear superiority, with reduced relative risk for treatment failure by 60% and significantly higher overall response rate (ORR) of 96% versus 90%, and prolonged duration of response [1]. These results were significant; however, cure cannot be guaranteed and still remains a therapeutic goal.

The particular radio sensitivity of lymphoid cells made radiation an attractive approach. Radioimmunotherapy (RIT) emerged as an option after Mo-Ab success, combining the selectivity of the anti-CD-20 immunotherapy with an attached radioisotope, making possible the delivery of radiation exactly within the tumor burden [2]. In 2002, the FDA approved the first radioimmunoconjugate (RIC) $^{90}$Y-Ibritumomab (Zevalin), and soon thereafter a second RIC $^{131}$I-Tositumomab (Bexxar) was approved, both efficient for the treatment of indolent or transformed, relapsed or refractory B-cell lymphoma [3].

$^{90}$Y-Ibritumomab tiuxetan ($^{90}$Y-IT) is a monoclonal IgG1κ anti-CD20 antibody attached to tiuxetan, a metal chelator who serves to stabilize the yttrium-90 radioisotope. It is a pure $\beta$-emitter that produces higher energy and longer path length radiation than $^{131}$I-Tositumomab, making it advantageous...
2 Patients and Methods

We have created a clinical protocol conducted by a multidisciplinary team formed by clinical hematologists, nuclear medicine physicians, radiopharmacy physicians, and nurses in the Miguel Servet University Hospital. It started in September 2005 and established the use of 90Y-IT in patients with an excisional biopsy confirming the diagnosis of CD20+ F-NHL grade 1, 2, or 3 according to the revised classification system of the World Health Organization (WHO), and who had relapsed or refractory disease after at least a first-line combined chemotherapy, patients had been diagnosed and treated within the same center. In 2007, the therapeutic inclusion was extended as consolidation after first-line chemotherapy in patients with complete or partial response confirmed by PET/CTscan.

Before undergoing into RIT consideration, all patients were thoroughly examined and had a complete blood count (CBC) with leukocyte differential and platelet count, positron emission tomography PET/CTscan, and bone marrow aspiration, and biopsy was carried out. They were also tested for general blood chemistry (including serum creatinine, liver function tests, uric acid, and lactate dehydrogenase).

Additional inclusion criteria applied to all cases were absolute neutrophil count (ANC) $\geq 1,500/\mu L$, absolute platelet count (APC) $\geq 100,000/\mu L$, and bone marrow total lymphocytes $\leq 25\%$ by morphological counting, also serum bilirubin $\leq 2.0\, \text{mg/dL}$ and serum creatinine $\leq 2.0\, \text{mg/dL}$. All patients were requested to sign an informed consent.

Response assessment was made 12 weeks after treatment; PET/CTscan was performed in all cases, and response criteria used were the same as the International Working Group (IWG). Subsequent follow-up evaluation also included CBC and physical examination every 3-4 months within the first 2 years after 90Y-IT therapy, and then every 6 months until relapse or death. A second PET/CTscan was performed at the first year of therapy, and a neck-chest and abdomino-pelvic CTScan was performed at the 5th year of 90Y-IT administration.

We assessed time to progression (TTP), overall response (OR) and OS in all patients. We also registered side effects, with special emphasis in myelotoxicity and emerging second neoplasms. OR was performed following the IWG criteria and classified as complete response (CR), partial response (PR), and no response (NR). TTP and OS were calculated from the date of 90Y-IT therapy until disease progression or death. All eligible patients were accepted by the clinical committee and included into the analysis. Patient data collection was cut-off at the last contact date. A database was created, and the statistical analysis of variables was performed with SPSS 15.0 program. Descriptive statistics,

### Complete blood count weekly until hematopoietic recovery

| Day 1 | Day 7 | 12th week |
|-------|-------|-----------|
| Rituximab 250 mg/m² | Rituximab 250 mg/m² + 90Y-IT 0.3-0.4 mCi/kg | PET/CTscan response evaluation |

**Figure 1: Therapeutic planning.**
Table 1: Patients characteristics (N = 65).

| Characteristic | Number | %   |
|----------------|--------|-----|
| Sex            |        |     |
| Male           | 29     | 55.4|
| Female         | 36     | 44.6|
| Age (years)    |        |     |
| Mean           | 61.45 years |
| Range          | 30–85 years |
| FLIPI          |        |     |
| Good           | 38     | 58.5|
| Intermediate   | 19     | 29.2|
| Poor           | 8      | 12.3|
| ECOG           |        |     |
| 1-2            | 22     | 96.9|
| Prior treatment|        |     |
| >2             | 26     | 4   |

CIs and Statistical analysis of patient characteristics, response rate, and adverse events were descriptive. Analysis of TTP and OS were performed on intent to treat basis and were calculated by the Kaplan-Meier method with CIs.

3. Results

Between September 2005 and February 2012 a total of 65 patients who met the previously defined eligible criteria were treated with ⁹⁰Y-IT in our hospital. 56 patients completed the follow-up and were considered into the analysis. Within demographic characteristics females were slightly more prevalent than males 55.4% (36) versus 44.6% (29). Mean age was 61.45 years (30–85), with overall good performance ECOG 0-1 in 96.9% of cases. The Ann Arbor stage distribution was IA 2 (3.1%); IIA 6 (9.2%); IIB 2 (3.1%); IIIA 5 (7.7%); IIIB 7 (10.7%); IV A 25 (38.5%); IVB 18 (27.7%). A total of 43 patients had bone marrow involvement at diagnosis. According to prognostic FLIPI score, the patient distribution was 58.5% (38) good, 29.2% (19) intermediate, and 12.3% (8) poor. 40% (26) patients had received more than two different combined chemotherapy schedules. According to status before ⁹⁰Y-IT therapy, the patients were classified as consolidation after first-line therapy 22 (33.84%), relapsed with more than 12 months after previous therapies 31 (47.69%), refractory to rituximab schedules 7 (10.77%), and partial response after first-line therapy 5 (7.70%). Main patients characteristics are detailed on Table 1. Table 2 details previous schedules received by consolidation group.

Orr was 94.6% (53/56). CR was achieved in 85.7% (48/56) patients. CR according to disease status before treatment is presented in Table 3. CR in relapsed disease 90% (27/30 valuable patients), in refractory disease 42.8% (3/7), in consolidation with CR after first-line therapy: 92.8% (13/14 valuable patients), and 100%(5/5) of patients that were in PR after first-line induction therapy converted to CR. PR was seen in 8.9% (5/56 valuable patients) and only 3 had no response. 16% (9/56) were non valuable patients, 8 were still within the first 12 weeks after ⁹⁰Y-IT infusion, and 1 contact loss. According to bone marrow involvement 90.5% of patients obtained a complete response (38 of 42 patients).

Mean TTP in patients with relapsed disease was 52.56 months (CI 95%: 42.31–62.81), with refractory disease 12.43 months (CI 95%: 7.86–17), consolidation in CR after first-line induction therapy was 38.81 months (CI 95%: 32.87–44.76), and consolidation in PR after first-line induction therapy was 27.25 months (CI 95%: 14.75–39.75). By the end of the study 28.5% (16) have relapsed (Figure 2). Overall mean TTP was 52.65 months (SD+ 5.03, CI 95%: 43.83–61.48) (Figure 3). The mean estimated OS was 63.86 months (CI 95%: 57.22–70.48) (Figure 4). Median estimated for OS and global TTP could not be calculated because of the good response of our patients at a median follow-up time of 57 months (range 2–73).

We recorded side effects for safety assessment. Asthenia was the most frequent nonhematological adverse event presented in 50% of patients. Grade 3-4 thrombocytopenia was the most frequent hematological toxicity presented in 35.7% 40 patients, with a median time of onset around the 6th week after ⁹⁰Y-IT infusion and spontaneous recovery around 8th week. 19% of patients developed grade 3-4 neutropenia within 4 weeks after ⁹⁰Y-IT infusion, and 17 patients had platelet transfused. One patient developed grade 2 mucositis. None of the patients required hospitalization. Four patients had concomitant neoplasm at the time of treatment (colon, lung, breast, and prostate), and one patient developed prostate neoplasm four years after treatment at the age of 75. There was no treatment related mortality.
4. Discussion

$^{90}$Y-IT therapy has proven to be efficient achieving complete and durable response rates including pretreated and rituximab refractory F-NHL patients, but there are not many long term studies using this approach in relapsed/refractory follicular non-Hodgkin lymphoma patients and consolidation [4, 5, 7–9].

The previous reported ORR on patients with relapsed/refractory follicular non-Hodgkin lymphoma receiving $^{90}$Y-IT therapy is as high as 73%, and TTP as long as 3 or more years with even long-term responders reported (>5 years) [9]. The study published by Zinzani et al. in a single center with 57 patients evaluated the long-term outcomes of $^{90}$Y-IT and reported ORR of 93% at a median followup of 48 months and CR as high as 70% [10]. The median duration of response is estimated in 14.2 months [4] and more than 20 months [10] in two different publications. In our study the median duration of response was 27 months. In regard to consolidation therapy, the study FIT randomized phase III trial demonstrated a clear prolongation in TTP, higher response rates, and improvement of response in partial responders [5, 11], emerging the need of further investigation to establish a well defined therapeutic approach.

The results obtained in our experience can be equalized with those previously reported elsewhere [10–15]. The CR achieved was 85.7%; overall TTP was around 52.65 months, with a mean estimated OS of 63.86 months and a mean follow-up time of 57 months (range 2–73), even in patients with bone marrow involvement at diagnosis. It seems that RIT with $^{90}$Y-IT in early stage of treatment induces higher and maintained CR, TTP, and OS (Figure 3). The evaluation of response to RIT, assessed by FDG-PET, has been reported as a main predictor of PFS, being PET/CT scan result post-RIT the only independent predictive factor [15].
$^{90}$Y-IT was a good-tolerated and low-toxic therapy for the majority of patients, even for those heavily treated. The adverse events and myelotoxicity presented were expected, manageable, and transient, and there were none major side effects or related mortality, making it safe for outpatient administration and even suitable for elderly patients.

5. Conclusion

The addition of $^{90}$Y-IT into F-NHL treatment improves response and progression free survival of disease, both as part of relapsed or refractory disease, and as consolidation therapy after first-line induction treatment. Yet, still there is not unified criteria of the best approach and timing of RIT incorporation into treatment, and which chemotherapeutic associations can offer better response at less toxicity. This field needs further investigation in order to adequate RIT into schemes and take advantage of what seems a promising therapeutic tool.

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