Long-term efficacy and toxicity results of the FLUMIZ trial (fludarabine and mitoxantrone followed by yttrium-90 ibritumomab tiuxetan in untreated follicular lymphoma)

The radiosensitivity of lymphomas as well as the local targeted delivery of high doses of radiation make radioimmunotherapy (RIT) an attractive therapeutic option. RIT is indeed an underestimated tool. In follicular lymphoma (FL), RIT represents one of the most effective single agents. The two most commonly used radioimmunoconjugates are ^{90}Y-ibritumomab tiuxetan (Zevalin®) and ^{131}I-tositumomab, both based on murine anti-Cd20 antibodies.

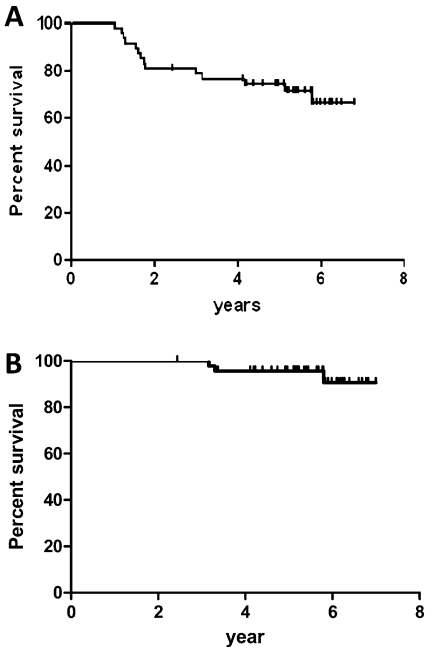

Figure 1. Progression-free survival (A) and overall survival (B).

RIT has demonstrated efficacy in relapsed/refractory FL and was approved for this indication [1]. Subsequently, many trials have evaluated the role of RIT consolidation after initial tumor debulking with chemotherapy or immunochemotherapy [2] and several phase II studies supported these results [3–5].

We now report updated long-term efficacy and toxicity results of a multicenter nonrandomized phase II trial of fludarabine and mitoxantrone plus RIT (fludarabine, mitoxantrone, zevalin trial), demonstrating that this combination was safe and very effective in untreated FL patients.

Sixty-one patients with stage III and IV untreated FL were enrolled between June 2004 and April 2006, at 13 Italian institutions. Briefly, treatment schedule was the following: 40 mg/m^2 oral fludarabine (F) on days 1–3, 10 mg/m^2 i.v. mitoxantrone (N) on day 1 every 28 days for six cycles (FN regimen), followed by one course of Zevalin®, which consisted in 2 weekly infusions of 250 mg/m^2 rituximab followed by a weight-based dose of ^{90}Y-ibritumumab tiuxetan. Primary end points at the time of the first analysis were complete response and hematological toxic effects, and secondary end points were overall survival (OS) and progression-free survival (PFS). Fifty-seven patients were treated with RIT after the completion of six courses of FN regimen (four patients were excluded due to disease progression and bone marrow infiltration >25%). Median follow-up at the time of the last analysis was 64 months (range 35–87). Six-year PFS was estimated to be 68.0% (Figure 1A), and 6-year OS was estimated to be 93.0% (Figure 1B). Noteworthy, late hematological side effects such as myelodisplastic syndromes or acute myeloid leukemias did not occurred so far. All patients had a complete hematological recovery after the completion of the sequential treatment. Sixteen patients relapsed during the follow-up period and four patients died due to disease progression. Twenty-two patients (38%) are in continuous complete remission after >4 years of follow-up. All relapsed patients underwent second-line chemotherapy and high-dose chemotherapy (stem cell rescue was performed in four patients).

These results confirm the long-term efficacy and safety of six cycles of fludarabine and mitoxantrone followed by consolidation with ^{90}Y-ibritumumab tiuxetan: the 6-year PFS and OS are comparable to the ones reported for chemoimmunotherapy alone in untreated FL and no increased incidence of secondary hematologic malignancies was observed. Consolidation with RIT is an innovative treatment approach which increases the rate of complete remission and maximizes the length of first remission.

In particular, in this study, sequential treatment with fludarabine-containing regimen and RIT did not give rise to cumulative toxicity, in terms of a good hematologic recovery and, overall, of a significant possibility of mobilizing the peripheral stem cells.

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disclosure

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