SUPPLEMENTARY METHODS

The study was performed in 12 Spanish institutions. It was approved by the local and central committees and registered at the Clinical Trials Gov web-site (NCT00505232). All patients provided written informed consent before study entry. Patients were registered from February 2006 until July 2008 and were followed until September 2011.

Inclusion criteria and baseline assessment

Patients were considered eligible if they were between 18 and 70 years-old and diagnosed with MCL according the WHO classification (22). Cyclin D1 positivity of diagnostic lymph node or tissue was required for diagnosis. If only bone marrow was available, Fluorescence in situ hybridation (FISH) for the t(11;14))(q13;q32) translocation and immunophenotype with a CD19/CD20/CD5/CD23 panel, to rule out CLL, was needed.

Inclusion criteria were: stage II-IV, ECOG < 3; adequate renal and liver function (creatinine, total bilirrubine, AST and ALT <2.5 upper normal limits), left ventricular ejection fraction $\geq$ 50% and appropriate bone marrow function (hemoglobin ≥10 g/dl, absolute neutrophil count ≥1500/mm^3 and platelets ≥100000 /mm^3), unless due to infiltration by lymphoma.

Patients previously treated with antineoplastic agents and those with active infection or non-controlled important concomitant diseases were excluded. Other exclusion criteria were positive serology for HBV (hepatitis B virus), HCV (hepatitis C virus) and HIV (human immunodeficiency virus) and central nervous system involvement by lymphoma

Pre-treatment and follow up evaluation

Pretreatment evaluation included physical examination; blood count with differential analysis; serum chemistry analysis; serum LDH, β2-microglobulin and immunoglobulins; peripheral blood phenotype; whole body computed tomography (CT) scan; bone marrow biopsy and aspiration; colonoscopy; cavum exploration and gastroscopy if Waldeyer ring involvement, echocardiography and/or radionuclide ventriculography. FISH to detect t(11;14) and other cytogenetic abnormalities (del 13q14, +12, del 17p, del 11q22.3) were performed on bone marrow/ peripheral blood samples at the Hospital Universitario de la Princesa.

Complete disease evaluation was carried out before treatment, after the 4^{th} cycle and at the end of the induction treatment. After consolidation, disease assessment was evaluated every 4 months until the 2^{nd} year and every 6 months thereafter.

Treatment

Induction phase

Patients were scheduled to receive R-HyperCVAD therapy alternating with R-MA every 21 days as described by Romaguera et al (5). Amendments of protocol were performed when the first 6 patients completed their treatment and the number of induction cycles was fixed at 6, due to the high response rate observed after the 4^{th} cycle.

Cytarabine dose was reduced to 1 g/m^2 in patients older than 60 years, and methotrexate was reduced to 75% in patients with creatinine value of 1.5-2 mg/dl and 50% in those with 2-3 mg/dl. Dose adjustments for subsequent cycles were required in the following situations: platelet count between 75000-100000/mm3 or absolute granulocyte count between (AGC) 750-1000/mm3 on day 21 of each cycle, development of febrile neutropenia or non-hematotological grade 3 toxicity at any moment. Dose -1 level entailed reductions of 75% of cyclophosphamide, 60% of methotrexate and 60% of cytarabine.

Treatment was discontinued if the patient did not reach the required hematological recovery after 5 weeks, (neutrophils $\geq$ 1500/ mm3 and/ or platelets > 100.000/ mm3) or developed grade 4 infection, any grade 4 non hematological toxicity or severe bleeding. Patients with less than partial response (PR) after 4 cycles discontinued the treatment.

Support therapy with Peg- Filgastrim after each cycle and pneumocistis jirovecci prophylaxis was mandatory. Prophylaxis with antibiotic, antiviral and antifungal therapy, the use of erythropoietin and transfusions were allowed according to each participating center's policy.

Peripheral blood stem cell (PBSC) collection as back-up was mandatory in the first six patients and recommended for the rest of patients.

Consolidation phase

Consolidation with ^{90}Y-Ibritumomab-Tiuxetan was scheduled 12 weeks after the 6^{th} cycle. Patients received a first dose of Rituximab 250 mg/m^2 and a week later, a second infusion immediately followed by a single dose of ^{90}Y-Ibritumomab-Tiuxetan was administered. The drug was kindly provided by Bayer-Shering.

Initial dose for ^{90}Y-Ibritumomab-Tiuxetan was 0.3 mCi/kg, and dose escalation to 0.4 mCi/kg was planned, according to a 3+3 design if no unacceptable toxicity was observed.

The dose of ^{90}Y-Ibritumomab-Tiuxetan was fixed at 0,3mCi/ Kg, as five out of 6 patients had sustained neutrophils and/or platelets below 1500/mm3 and/ or 150000/mm3 respectively, beyond 12 weeks after the completion of induction therapy.

The infusion of the back up stem cells was recommended if grade 4 hematological toxicity was not treatable with supportive care or at the discretion of the physician in charge of the patient.

Study endpoints and definition of study variables

The main objective was to evaluate the feasibility, safety and efficacy of the whole treatment. Clinical efficacy was evaluated in terms of overall response (OR) and CR rates, FFS, PFS and OS.

Response criteria were assessed according to The International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (24). Patients without response assessment were considered non responders.

The toxicities of induction and consolidation treatment were evaluated according to the National Cancer Institute´s Common Toxicity criteria (CTCAE v3.0).

Failure free survival (FFS) was defined as the time from the date of study entry until date of recurrence, progression of disease, death from any cause or any toxic event that prohibited treatment according to protocol. Responding patients who did not complete the whole treatment due to personal reasons or whose treatment was delayed beyond recommended were censured in the moment this deviation occurred.

Off protocol responding patients who received any additional anti-lymphoma treatment were not considered failures, and were censored at the time of this new treatment.

Progression free survival (PFS) was defined as the time from the inclusion in the trial until progression, recurrence or death as a result of lymphoma**.**

Overall survival (OS) was defined as the interval between the date of study entry of inclusion in the trial until death from any cause.

All variables were calculated in the intent- to treat- population, defined as patients who had received at least one cycle of the chemotherapy regimen. For survival analysis all patients were followed until the closure of the study regardless of treatment discontinuation.

Statistical analysis

Sample size was calculated in order to estimate a feasibility rate of 70% (patients who complete the whole treatment schema), with a maximum error of 17.5% and 95% confidence level. The sample size was 27 patients and considering that 10% of patients would not be evaluable for efficacy for early drop-outs, the target for total enrollment was 30. Epidat v 3.1 program was used for calculations.

FFS, PFS, and OS were estimated using the Kaplan-Meier method (25) and were compared between groups by log-rank test. Tests were two-sided, and the level of statistical significance was a *P* value less than 0.05. Comparison between groups for categorical covariates was performed using the Fisher´s exact test. Statistical analysis was performed with the SPSS v 15.0 package.

The crude incidence of secondary malignancies was calculated as the proportion of patients diagnosed with secondary neoplasm in the whole population. The cumulative incidence was

estimated using a nonparametric method that considers death due to other causes as a competing risk (26). Stata v 12.1 program was used for calculations.