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Follicular non-Hodgkin's lymphoma: correlation between histology, pathophysiology, cytogenetic, prognostic factors, treatment, survival

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Abstract

Background: Folicullar lymphoma (FL) is one of the most common types of all non-Hodgkin's lymphomas (25–40%), characterized by a slowly progressive enlargement of lymph nodes, impairment of hematopoiesis, increased risk to infections, a relatively good prognosis, but usually incurable. Histopathologically, FL has been graded according to the proportion of centroblasts and stratified into grades 1–3: FL grade 1–2 (low-grade), which include cases with few centroblasts, and FL grade 3, divided into grades 3a and 3b, based on the absence of centrocytes in the latter category. Several studies have identified some differences between grade 3a and grade 3b of FL, with most cases of FL grade 3b being more closely related to diffuse large B-cell lymphoma (DLBCL) at molecular level. Several multicenter prospective randomized trials demonstrated an improved outcome when Rituximab (R) was added to chemotherapy for the treatment of follicular non-Hodgkin's lymphomas and a beneficial effect in the quality of life after Rituximab maintenance therapy at these patients. *Aim of study*: To establish some correlation between histology, prognostic factors, treatment and evaluate whether maintenance therapy with anti-CD20+ monoclonal antibodies prolonged progression free survival compared to observation only at the patients with follicular lymphomas treated with R-chemotherapy regimens. *Patients and Methods*: We studied nineteen patients with follicular non-Hodgkin's lymphomas (grades 1–3) treated with R-CHOP/R-miniCHOP regimens hospitalized in the Clinic of Hematology from Craiova (Romania), between 2008–2011. After these treatments, nine patients with stage III/IV follicular lymphomas were treated with Rituximab maintenance therapy (eight cycles Rituximab 375 mg/m^2, i.v., once every three months for two years) *vs.* observation only at 10 patients. *Results*: In our study, low-grade FL was correlated with a good prognosis at patients with FLIPI score 0–2; the statistical analysis revealed that the progression free survival (PFS) was prolonged at the patients with stage III/IV follicular lymphomas who received Rituximab maintenance therapy compared to the ones with observation only with 1.9 years. *Conclusions*: Low-grade (1–2) FL was correlated with a good prognosis in patients with FLIPI score 0–2; Rituximab maintenance therapy compared with observation only is safe and prolonged progression free survival at patients with follicular lymphomas treated with R-chemotherapy as first line therapy.

Keywords: follicular lymphoma, prognostic factors, Rituximab, maintenance therapy, survival.

Introduction

Folicullar lymphoma (FL) is one of the most common types of non-Hodgkin's lymphomas (25–40%), characterized by a slowly progressive enlargement of lymph nodes, an impairment of hematopoiesis, an increased risk to infections, with a relatively good prognosis, a median survival of up to 10 years, but usually incurable.

FL is more frequent at patients with median age 60 years, predominantly in females who are diagnosed in an advance stage of disease with rare B-symptoms and extranodal involvement.

Histopathologically, FL has traditionally been graded according to the proportion of centroblasts and stratified into three grades 1, 2, 3 (grade 1: 0–5 centroblasts/ microscopic field; grade 2: 6–15 centroblasts/microscopic field; grade 3: >15 centroblasts/microscopic field). The 2008 *WHO* classification lumps cases with few centroblasts as FL grade 1–2 (low-grade) and does not require or recommended further separation. FL grade 3 is divided into grades 3a and 3b, based on the absence of centrocytes in the latter category. Several studies have identified some differences between grade 3a and grade 3b of FL, with most cases of FL grade 3b being more closely related to diffuse large B-cell lymphoma (DLBCL) at the molecular level [1, 2]. Transformation of FL into an aggressive histology, more frequently diffuse large B-cell lymphoma, is an important event with high morbidity and mortality.

Immunohistochemical findings revealed in FL are: sIg+, CD20+, CD79a+, CD10+/-, Bcl-6+, Bcl-2+, CD23+/-, CD5-, CD43-, CD21+, Cyclin D1-.

The most important cytogenetic marker for FL is translocation t(14;18)(q32;q21) or variants t(2;18), t(18,22) present in 80% of cases; 20% present other additional chromosomal abnormalities such as partial 6q-, +7, +X, +12, +21, associated with histological progression.

Translocation between chromosome 14 and 18 leading to the fusion of Bcl-2 gene on chromosome18 to the gene for the immunoglobulin heavy chain on chromosome 14 leads to the overexpression of Bcl-2 and an impairment of apoptosis, *via* Bcl-2α and Bcl-2β proteins [3].

The evolution of follicular non-Hodgkin's lymphomas

is often characterized by remission after initial therapy followed eventually by relapse. Follicular lymphomas at patients with advanced disease are considered incurable and the main goal of first line treatment is to achieve sustained remission and prolonged progression free survival (PFS). The clinical course and response to therapy in follicular lymphoma is characterized by striking variability depending on a combination of different factors including disease site, age at diagnosis, stage at diagnosis, number of lymph nodes areas involved, chromosomal and genetic alterations and the presence of regulatory T-cells and macrophages, the levels of hemoglobin and lactate dehydrogenase (LDH) [4].

Many treatment approaches have been proposed for patients with FL including administration of Rituximab (R), a monoclonal antibody targeting the CD20 antigen on FL cells, or combinations of Rituximab and chemotherapy (R-CVP, R-CHOP, R-MCP) [5–7].

Several multicenter prospective randomized studies demonstrated an improved outcome when Rituximab was added to chemotherapy in FL and, in addition a beneficial effect in the quality of life after anti-CD20+ monoclonal antibodies maintenance therapy at these patients [8, 9].

The aim of the study was to establish correlations between histology, prognostic factors, treatment and to evaluate whether maintenance therapy with anti-CD20+ monoclonal antibodies prolonged progression free survival compared to observation only at the patients with follicular lymphomas treated with R-chemotherapy regimens.

Patients and Methods

This study is a retrospective analysis on nineteen patients with III/IV stages of follicular non-Hodgkin's lymphomas (informed consent obtained) hospitalized in the Clinic of Hematology from Craiova, Romania, between 2008–2011, treated as first line therapy with eight cycles R-CHOP (Rituximab–Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) or R-miniCHOP, given every three weeks. Patients received eight cycles R-CHOP – 36% (patients with a lower median age at baseline – 46 years *vs.* 76 years patients who have received R-miniCHOP, B-symptoms, bulky adenopathy in the chest or abdomen, cytopenias, without cardiac diseases) or eight cycles R-minidose of CHOP – 64% (patients with a higher median age – 76 years, with mild-moderate cardiac diseases). All patients were biopsied and histopathological exam has been graded according to the proportion of centroblasts and centrocytes and stratified in grade 1, 2 or 3. Immunohistochemical analysis was made in all cases. All patients were observed by blood tests (complete blood cell count, serum chemistry profile, serum immunoglobulins, lactate dehydrogenase), ultrasound examination of the abdomen or computed tomography of the chest and abdomen, echocardiography and electrocardiography. The tests were performed at three months for the first two years after completion of initial treatment and at six months intervals there after.

Prognostic factors were evaluated by *Follicular Lymphoma International Prognostic Index* (FLIPI), which included five parameters: age (>60 *vs.* ≤60 years), stage of disease (III/IV *vs.* I/II), anemia (Hb <120 *vs.* ≥120 g/L), number of lymph node areas (>4 *vs.* ≤4), LDH (increased *vs.* normal) [10].

We followed the side effects of the treatment and the response status after induction therapy. After induction therapy, nine of the patients were treated with Rituximab maintenance therapy (eight cycles Rituximab 375 mg/m^2, i.v., once every three months, for two years) *vs.* observation only at 10 patients.

The statistical methods used included Kaplan–Meier survival curves and a calculation of a *p*-value.

Results

The median age at diagnosis was of 61 years, 58% of patients were females and 42% males; nine of the patients had Ann Arbor stage III disease and 10 had stage IV disease at the time of diagnosis, 52% bone marrow involvement, 46% B-symptoms, 63% elevated LDH. Fifteen patients have been low-grade follicular lymphoma (one of them – grade 1 and 14 – grade 2) and four patients have had grade 3 follicular lymphoma (three cases – grade 3a and one case – grade 3b) (Figures 1–8). Immunohistochemical analysis had been made in all patients and revealed in most cases: L26/CD20+, Bcl-6+, Bcl-2+, CD10+/-, CD23+/-, CD5-, CD21+, Cyclin D1-, Ki67+.

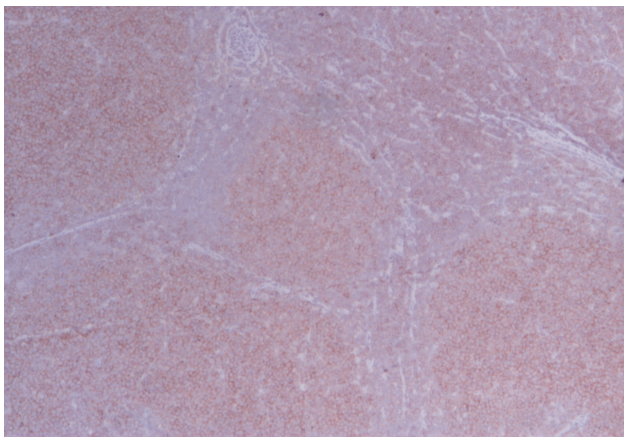

Figure 1 – ***Lymph node biopsy: grade 1 FL CD10+ (IHC for CD10, ob. 4×).***

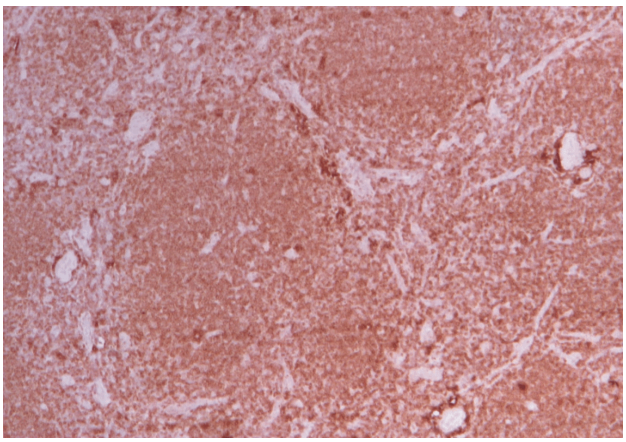

Figure 2 – ***Lymph node biopsy: grade 1 FL Bcl-2+ (IHC for Bcl-2, ob. 4×).***

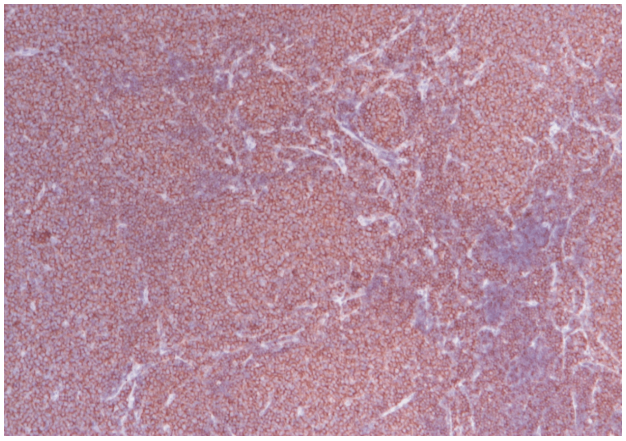

Figure 3 – ***Lymph node biopsy: grade 2 FL CD20+ (IHC for CD20, ob. 4×).***

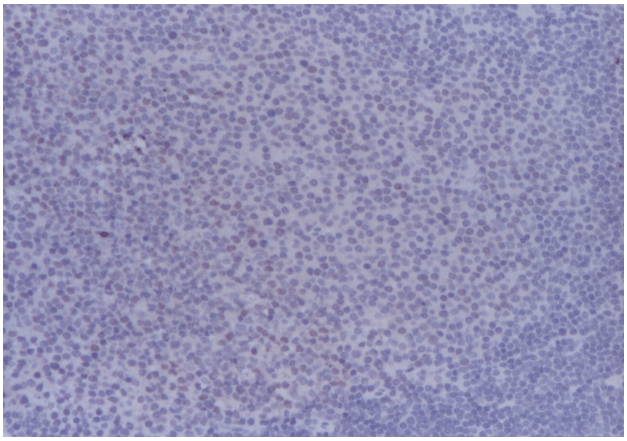

Figure 4 – ***Lymph node biopsy: grade 2 FL Bcl-6+ (IHC for Bcl-6, ob. 4×).***

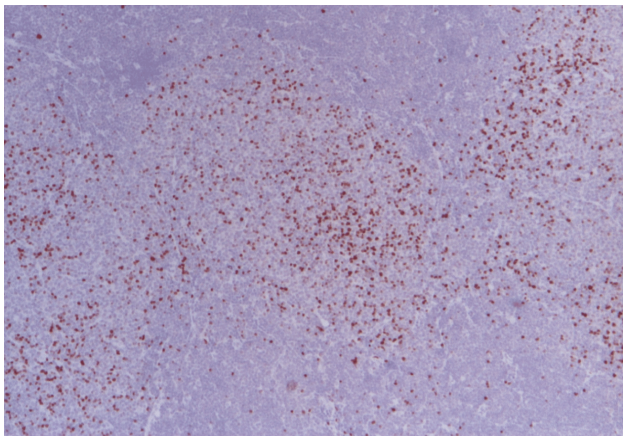

Figure 5 – ***Lymph node biopsy FL Ki67+ 20% (ob. 4×).***

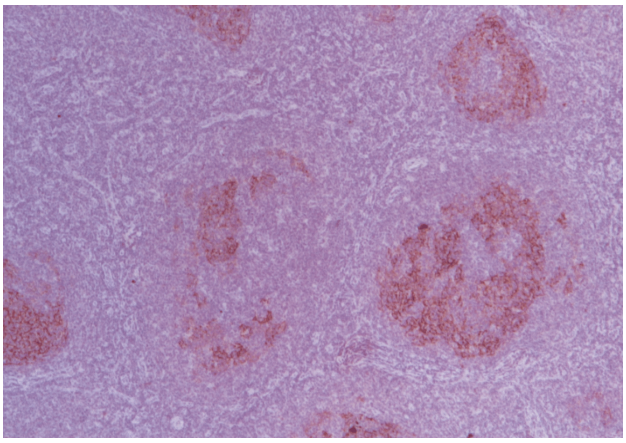

Figure 6 – ***Lymph node biopsy FL CD23+ (ob. 4×).***

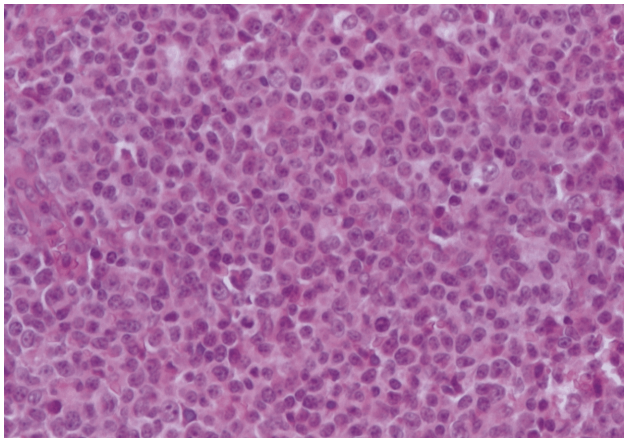

Figure 7 – ***Lymph node biopsy: grade 3a FL (HE stain, ob. 40×).***

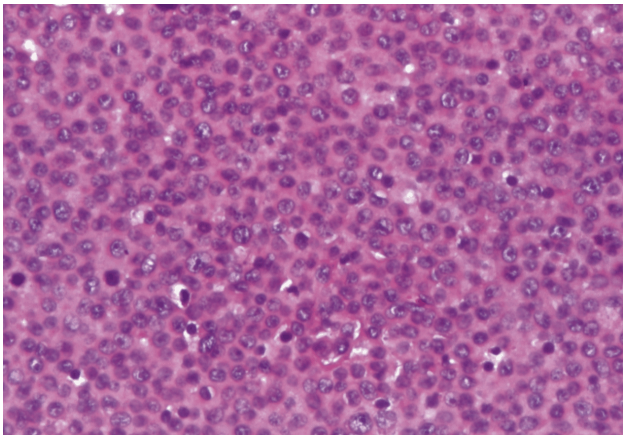

Figure 8 – ***Lymph node biopsy: grade 3b FL (HE stain, ob. 40×).***

Six patients developed mild-to-moderate hypogammaglobulinemia. IgA levels were normal at all patients from diagnosis of follicular non-Hodgkin's lymphomas to the end of the study, two patients had a decline in IgM levels and five patients had a decline in IgG levels over the same period; three patients developed severe leukopenia with neutropenia, two of them with severe infections; one patient had urticaria; 16.5% had a FLIPI score 0–1, 49.5% FLIPI score 2, 34% FLIPI score 3–5. The response status was: complete response 66%, partial response 22%, other 12%. The grade 3b follicular lymphoma has been transformed in diffuse large B-cell lymphoma.

Nine patients with follicular lymphoma grade 2 received eight cycles Rituximab – 375 mg/m^2, i.v., once every three months for two years *vs.* observation only at 10 patients (patients with a higher median age – 76 years, with severe cardiac diseases, who developed moderate hypogammaglobulinemia, severe leukopenia with neutropenia or gastrointestinal hemorrhage; two patients refused to continue maintenance therapy with Rituximab after induction therapy with R-CHOP). The progression free survival was prolonged to the patients with stage III/IV follicular lymphomas who received Rituximab maintenance therapy – 3.6 years – compared to observation only group – 1.9 years (p<0.0001) (Figure 9).

At four years, overall survival was 88% *vs.* 80% for Rituximab maintenance and observation, respectively.

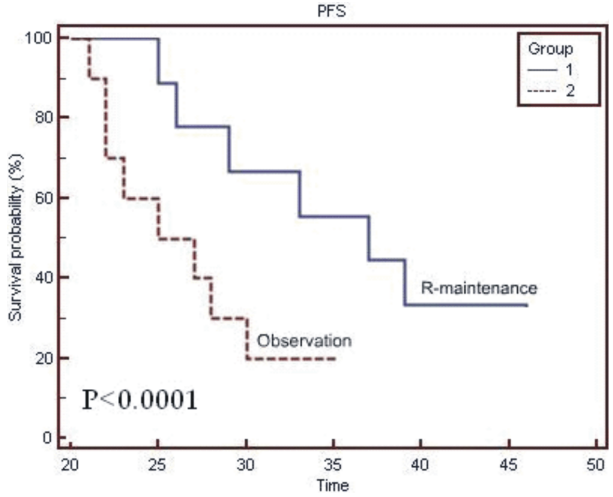

Figure 9 – ***Progression free survival at patients with follicular lymphoma: stage III/IV.***

Discussion

FL is usually diagnosed at an advanced stage and has had a long clinical evolution, characterized by remission after initial therapy followed by relapse. Transformation in an aggressive non-Hodgkin's lymphoma, frequently diffuse large B-cell lymphoma, appears in 3% rate per year [11–13].

Correlation between histological grade and overall survival is controversial. Although there are not important differences between overall survival at patients with grade 1–2 FL, in grade 3 FL survival is significantly decreased, according to some studies [14–16]. Other studies did not find significant differences between the three histological grades about overall survival [17].

FL low-grade is more probable to be CD10+ and to have t(14;18) compared to grade 3b FL which can be similar to a diffuse large B-cell lymphoma, and Bcl-6 appears with a similar frequency. The proliferation index is correlated with the histological grade and overall survival and has prognostic value. Bcl-2 gene and Bcl-2 proteins family have a central role in apoptosis. A great number of MCL1+ centroblasts is correlated with a decreased overall survival. Bcl-6 level is correlated with a favorable prognosis in FL. Expression of protein PU.1 represent a favorable marker for overall survival, regardless of FLIPI. TP53 mutation was associated with transformation and decreased overall survival. SOCS3, a cytokinic suppressor, and over-expression Ying-Yang 1, a „Zn–fingers" protein which regulated IL-4 gene expression, are unfavorable prognosis factors in FL. FL without t(14;18) are less probable to express CD10 or Bcl-2 and a better overall survival. Other chromosomal abnormalities were associated with a shorter survival. Histological transformations varied between 5–60%, varied function by LDH increasing and involvement of disease in unusually extranodal areas. FLIPI score represent a prognostic factor to the patients treated with immunochemotherapy, may be applied after the first relapse and predict for transformation [15].

The anti-CD20 monoclonal antibody sensitizes lymphoma cells to chemotherapy and interacts with the host's immune system; Rituximab is very effective in mediating fixation of the complement cascade, growth arrest and apoptosis in some non-Hodgkin's lymphomas cell lines [17].

Several multicenter prospective randomized studies revealed a beneficial effect in quality of life and prolonged progression free survival when the patients received Rituximab maintenance therapy after R-CVP or R-CHOP as first line therapy at the patients with follicular lymphomas.

ECOG 1496 study compared patients with stage III/IV indolent lymphomas randomized to receive Rituximab maintenance therapy (375 mg/m^2 weekly ×4 then every six months for two years) or observation, following CVP induction therapy; 157 patients of 305 evaluable were randomized to Rituximab maintenance therapy and 148 were randomized to observation only; the median progression free survival was significantly longer in the Rituximab group compared to the observation group (HR: 0.4; median progression free survival was estimated at 4.3 years *vs.* 1.3 years from maintenance randomization for Rituximab and observation, respectively [18].

EORTC 20981 study compared Rituximab maintenance therapy after R-CHOP in relapsed/ refractory follicular non-Hodgkin's lymphomas with observation only; 465 patients were randomized to induction with six cycles of CHOP or R-CHOP; those in complete or partial remission were randomized to maintenance with Rituximab 375 mg/m^2, i.v., once every three months for two years, or observation. Rituximab maintenance therapy prolonged median progression free survival from second randomization of 51.5 months *vs.* 14.9 months with observation only (HR: 0.4; p<0.0001) [19].

The *German Low Grade Lymphoma Study Group* trial compared the patients with relapsed/refractory low-grade lymphomas who received Fludarabine, Cyclo-phosphamide and Mitoxantrone (FCM) alone or with Rituximab; patients with a CR/PR were further randomized to receive therapy with either two courses of Rituximab at three and six months after salvage treatment or observation only. The median PFS for the group with Rituximab was not reached at three years; the estimated median PFS was 21 months in the group that did not receive Rituximab [20].

The recent results of the *Primary Rituximab and Maintenance* (PRIMA) trial revealed that maintenance treatment with Rituximab for two years was associated with an increased PFS of 82% *vs.* 66% in the placebo patients group at 25 months (p<0.001) [8].

Watanabe T summarized the current knowledge on therapies for treatment of follicular lymphomas: traditional therapies, a series of phase III trials comparing the effect of Rituximab + chemotherapy *vs.* chemotherapy alone, which indicated significant improvements in PFS for Rituximab + chemotherapy [5–7, 21]; a series of studies comparing maintenance therapy using Rituximab or interferon after completion of first line treatment with Rituximab *vs.* observation alone, which indicated prolonged response durations

and PFS [8, 9, 22]; various therapies included novel monoclonal antibodies (TLR-9, Bendamustine, Veltuzumab, Epratuzumab, Inotuzumab, Galiximab) [23–25]; immunoradiotherapy (^{90}Yttrium–Ibritumomab Tiuxetan or ^{131}Iodine–Tositumomab), idiotype vaccines.

In our retrospective analysis, the progression free survival was prolonged at patients with stage III/IV follicular lymphomas who received Rituximab maintenance therapy to 3.6 years *vs.* 1.9 years with observation only. These results were concordant with the results published in the mentioned studies. Rituximab is generally well tolerated; hypersensitivity reaction is rare and appears at first dose; other side effects are: leukopenia, granulocytopenia, fever, chills, rash, urticaria, infections, hemorrhage, hypogammaglobulinemia. Our patients developed: mild to moderate hypogammaglobulinemia – six patients; severe leukopenia with neutropenia – three patients, two of them with severe infections; one patient had urticaria. Severe leukopenia with neutropenia correlated with severe infections was more frequently observed after R-CHOP.

Conclusions

In this study, low-grade FL was correlated with a good prognosis at patients with FLIPI score 0–2, nine of them are in complete response and three in partial response at the right moment. Our experience confirms the results of several multicenter prospective randomized studies that compared Rituximab maintenance therapy to observation only. Rituximab maintenance therapy was safe and prolonged progression free survival at patients with follicular lymphomas treated with R-chemotherapy regimens as first line therapy, to 3.6 years *vs.* 1.9 years with observation only. This experience can serve as a start for long-term management of the patients with maintenance Rituximab therapy and a cost-effectiveness analysis of this treatment at our population.

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