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Similar prognosis of transformed and *de novo* diffuse large B-cell lymphomas in patients treated with immunochemotherapy☆

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ABSTRACT

Background: The prognosis of diffuse large B-cell lymphomas (DLBCL) transformed from indolent lymphoma (TL) has been considered poorer than that of *de novo* DLBCL. However, it seems to have improved since the introduction of rituximab.
Patients and methods: We compared the characteristics (including the cell-of-origin), and the prognosis of 29 patients with TL and 101 with *de novo* DLBCL treated with immunochemotherapy.
Results: Patients with TL and *de novo* DLBCL had similar characteristics. All TL cases evolving from follicular lymphoma were germinal-center B-cell-like, while those TL from marginal zone lymphoma or chronic lymphocytic leukemia were non-germinal-center B-cell-like. The complete response rate was similar in TL and *de novo* DLBCL (62 *vs.* 66%, $p = 0.825$). The 5-year overall and progression-free survival probabilities (95% CI) were 59% (40–78) and 41% (22–60) for TL and 63% (53–73) and 60% (50–70) for *de novo* DLBCL, respectively ($p = 0.732$ for overall survival and $p = 0.169$ for progression-free survival).
Conclusion: In this study, the prognosis of TL and *de novo* DLBCL treated with immunochemotherapy was similar. The role of intensification with stem cell transplantation in the management of TL may be questionable in the rituximab era.

Pronóstico similar de los linfomas transformados y los linfomas difusos de células B grandes *de novo* en pacientes tratados con inmunoquimioterapia

Palabras clave:
Linfoma transformado
Inmunoterapia
Quimioterapia
Pronóstico

RESUMEN

Antecedentes: El pronóstico de los linfomas difusos de células B grandes (LDCBG) transformados de linfomas indolentes (LT) ha sido considerado más desfavorable que el pronóstico de LDCBG *de novo*. Sin embargo, este parece haber mejorado desde la introducción de rituximab.
Pacientes y métodos: Se compararon las características (incluyendo la célula de origen) y el pronóstico de 29 pacientes con LT y 101 con LDCBG *de novo* tratados con inmunoquimioterapia.
Resultados: Los pacientes con LT y LDCBG *de novo* tenían características similares. Todos los casos de LT que evolucionaron de un linfoma folicular fueron linfomas de células B de tipo centro germinal, mientras que aquellos LT que evolucionaron de un linfoma de la zona marginal o leucemia linfocítica crónica fueron de tipo no centro germinal. El índice de respuesta completa fue similar en los LT y en los LDCBG *de novo* (62 frente a 66%, p = 0,825). Las probabilidades de supervivencia global y libre de progresión a 5 años (IC 95%) fueron del 59% (40–78) y el 41% (22–60) para LT y del 63% (53–73) y el 60% (50–70) para LDCBG *de novo*, respectivamente (p = 0,732 para supervivencia global y p = 0,169 para supervivencia libre de progresión).

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Conclusión: En este estudio, el pronóstico de los LT y LDCBG *de novo* tratados con inmunoquimioterapia fue similar. El papel de la intensificación con trasplante de precursores hematopoyéticos en el tratamiento del LT puede ser cuestionable en la era del rituximab.

Introduction

Diffuse large B-cell lymphomas (DLBCL) transformed from low-grade lymphoproliferative neoplasms (TL) have historically been associated with an aggressive course and poor prognosis.[1,2] Nonetheless, some studies in the immunochemotherapy era have reported an improvement in the prognosis of these neoplasms.[3–5]

In the pre-rituximab era several studies showed a markedly better prognosis in TL patients receiving consolidation treatment with high-dose chemotherapy and autologous stem cell transplantation (ASCT) than those receiving only chemotherapy.[6,7] However, following the introduction of rituximab the survival of patients with TL has improved, being similar to that of *de novo* DLBCL, regardless of the administration of consolidation chemotherapy and ASCT.[4,8,9]

Although most TL studies have focused on transformation from follicular lymphoma (FL) (2–3% per year),[1,2,8] other indolent lymphoproliferative neoplasms, such as marginal zone lymphoma (MZL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), can also transform into DLBCL. The frequency of transformation from MZL, including splenic MZL and nodal MZL, into DLBCL ranges between 5% and 10%,[10–12] with scarce data available on its prognosis in the rituximab era.[13] Of note, there are reports of selected gastric MALT cases evolving to DLBCL[14] successfully treated with only eradication treatment of Helicobacter pylori by antibiotics. Conversely, it is well known that Richter syndrome (transformation of CLL into a high-grade lymphoma) responds poorly to treatment and entails a particularly bad prognosis.[15]

The pathobiological characteristics and clinical outcome of DLBCL are heterogeneous with 3 major groups correlated with outcome having been identified according to their cell-of-origin (COO) by gene expression profiling (GEP): germinal center B-cell-like (GCB), activated B-cell-like (ABC), and unclassified.[16] Several algorithms have been developed using immunohistochemical markers in an attempt to reproduce the GEP results and establish the COO using more readily available technology. The Hans algorithm is most commonly used and it classifies DLBCL into GCB and non-GCB. With this method, some groups have identified the COO as an independent prognostic factor for survival in DLBCL,[17–18] while others have not.[19,20] To our knowledge, in the rituximab era few studies have analyzed both the survival and the prognostic influence of the COO in TL, particularly TL from low-grade lymphomas other than FL.

Therefore, in the present study we compared the clinical and biological features (including the COO) as well as the prognosis of TL and *de novo* DLBCL treated with immunochemotherapy in a single institution.

Patients and methods

Patients

The records of 163 consecutive *de novo* DLBCL and 31 TL diagnosed from 2003 to 2012 in our institution were reviewed. Only patients treated with immunochemotherapy were selected. In all cases, the diagnosis was made by tissue biopsy. Patients with HIV-infection, those from whom a biopsy specimen was unavailable for revision and patients with specific subtypes of DLBCL such as primary cutaneous DLBCL, primary central nervous system lymphoma or primary mediastinal DLBCL, were excluded from the study.

The main clinical and biological data were collected, as were the treatment and outcome of both the prior low-grade and the high-grade lymphoma. The COO was established by means of the Hans algorithm, which uses the imunohistochemical expression of CD10, BCL6 and MUM1 on formalin-fixed-paraffin-embedded tissue sections to classify DLBCL into GCB and non-GCB.[17]

TL was defined as biopsy-proven DLBCL in patients with a previous diagnosis of a low-grade lymphoproliferative disorder (FL, CLL, MZL) or as cases with both DLBCL and a low-grade lymphoproliferative disorder diagnosed at the same time (in the same or another lymph node). This latter situation, known as composite lymphoma, is often considered TL at diagnosis,[6,20,21] based on the molecular evidence of a clonal relationship between DLBCL and FL.[22,23] The study received institutional approval by the ethical committee of Germans Trias I Pujol Hospital (code LT2015).

Statistical analysis

Baseline demographic and clinical and biological characteristics are presented as median and range for continuous variables and frequency and percentage for categorical variables. Comparisons of these variables between patient groups were performed by the χ^2, the Fisher's exact, Student's-*t* or Mann–Whitney's *U* test, as appropriate.

Complete response criteria were according to previously reported.[24] Time to transformation (TTT) was defined as the time interval between the diagnosis of the low-grade lymphoma and the diagnosis of TL. Progression-free survival (PFS) was defined as the time from diagnosis to relapse, progression or death due to any cause. Overall survival (OS) was defined as the time from diagnosis to the time of death by any cause.[24]

The Kaplan–Meier method was used to calculate the OS and PFS curves, and the log-rank test was used to compare the survival between groups (TL and *de novo* DLBCL). The variables that showed a difference between the two groups with a p value <0.2, and were considered clinically relevant, were also included to perform the multivariate analyses using Cox's proportional hazards regression model. All these studies were performed using SPSS v15.0 software (IBM, Somer, NY).

Results

Patients

Of 163 patients with *de novo* DLBCL, 22 were excluded because of HIV-positive status and 29 because the diagnostic tissue sample was not available for revission. Three patients with primary cutaneous DLBCL leg type, 2 with primary mediastinal DLBCL and 6 patients not treated with immunochemotherapy (including 4 primary CNS lymphomas) were also excluded from the study. Of 31 TL, 2 patients were excluded because they were not treated with immunochemotherapy. One-hundred and one *de novo* DLBCL and 29 TL were finally included in the study. Of the 29 TL, 10 were composite lymphomas (considered as TL at diagnosis), 9 had a previous diagnosis of FL, 6 of MZL and 4 of CLL. As shown in Table 1, there were no differences between the two groups, other than CD10-positivity. International prognostic index (IPI), a score that encompasses the most important clinical and analytical prognostic variables and which defines broadly different prognostic groups,