Inclusion of Rituximab in Treatment Protocols for Non-Hodgkin's Lymphomas and Risk for Progressive Multifocal Leukoencephalopathy

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Evaluate the application of risk estimates of progressive multifocal leukoencephalopathy to your patients with non-Hodgkin's lymphoma previously treated with rituximab.
2. Include progressive multifocal leukoencephalopathy in the differential diagnosis for neurological symptoms in your patients with non-Hodgkin's lymphoma previously treated with rituximab.

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ABSTRACT

Objectives. Rituximab is an anti-CD20 monoclonal antibody that promotes better treatment outcomes in pa-

tients with non-Hodgkin's lymphoma (NHL). Case series of progressive multifocal leukoencephalopathy

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(PML) in patients receiving rituximab within polychemotherapy regimens have led to the introduction of a black box warning, but no risk estimation has ever been provided.

Methods. We performed a retrospective, monocentric cohort study on 976 NHL patients diagnosed in 1994–2008, including 517 patients who received at least one dose of rituximab.

BACKGROUND

Recently, the monoclonal antibodies natalizumab and efalizumab were associated with progressive multifocal leukoencephalopathy (PML) among HIV⁺ patients with different autoimmune disorders [1–3]. Rituximab is an anti-CD20 monoclonal antibody currently employed for treatment of patients with non-Hodgkin's lymphoma (NHL) and several autoimmune disorders [4]. Despite the fact that large case series have suggested a link between PML and rituximab [5], the risk remains undetermined.

We recently reported six cases of PML in HIV⁺ hematological patients (including five NHL cases) treated with rituximab at the Hematology Unit of the University Hospital of Pisa [6, 7], establishing an incidence rate of 2.89 cases per 100,000 patient-years [8]. This value is about twofold higher than that reported for AIDS patients (the population traditionally carrying the highest risk for PML) in the late highly active antiretroviral therapy period [9]. In order to assess whether, and to what extent, rituximab contributed to such a high incidence of PML, we report here an analysis of PML risk in HIV⁺ NHL patients exposed to standard chemotherapy regimens that included rituximab or not.

METHODS

Patients were selected from the Electronic Clinical Registry of the Hematology Unit at the University Hospital of Pisa. As of October 1, 2008, the registry (established in 1994) contained the clinical records of 12,291 patients. Subjects were included in the analysis if they had received a diagnosis of NHL (other than B-chronic lymphocytic leukemia), tested negative for HIV during follow-up, and were followed up for ≥ 6 months. The follow-up period was defined as the time interval ranging from the diagnosis of NHL to the occurrence of PML, death, or last recorded visit. The following data were recorded for each patient: gender, age at the time of NHL diagnosis, type of NHL, stage at diagnosis, and requirement for neurology-oriented procedures (at least one brain computed tomography scan, magnetic resonance imaging [MRI], or neurologic consultation) during the follow-up. The latter variable was used as a proxy

Results. Inclusion of rituximab into standard chemotherapy regimens for NHL caused a significantly higher incidence of PML cases (rate difference, 2.2 every 1,000 patient-years; 95% confidence interval, 0.1–4.3).

Interpretation. Based on this finding, clinical surveillance of PML-related symptoms is recommended in NHL patients exposed to rituximab. *The Oncologist* 2010; 15:1214–1219

for PML awareness, expected to be lower before the natalizumab affair and resulting in a possible notoriety bias.

NHL cases were grouped as early (Ann Arbor stage I or stage II) or advanced disease (Ann Arbor stage III or stage IV) [10] and as low- or high-grade in accordance with the World Health Organization classification [11]. PML cases were included only when the diagnosis was supported at least by MRI, according to consensus terminology [12]. Exposure to rituximab was defined as at least one dose of rituximab received during the study period.

The risk for PML was calculated as the rate difference (RD) between rituximab-exposed and unexposed patients, rather than the rate ratio, because the rate ratio can be very high when the numerator approaches zero (in rare diseases such as PML) [13–15]. The unadjusted RD, adjusted RD, and respective 95% confidence intervals were calculated as suggested by Armitage et al. [16]. The adjusted RD was computed by means of direct standardization. The sum of the person-years calculated for the two groups (exposed plus unexposed to rituximab) was used as the standard population. Stratification was made using quartiles of a propensity score computed by multiple logistic regression, using as covariates those variables (gender and age) showing statistically significant differences ($p < .05$) on univariate analysis. Mean values were compared using Student's *t*-test, whereas proportions were compared using χ^2 tests. The SPSS software package, version 14 (SPSS Inc., Chicago, IL), was used for statistical analyses.

RESULTS

The inclusion criteria allowed the selection of 976 patients with NHL. Overall, 517 patients received at least one rituximab dose (375 mg/m²) during the follow-up period. The median number of doses of rituximab administered in this group was four (range, 1–27). The numbers of patients diagnosed with NHL before 1998 (year of rituximab approval by the Italian regulatory agency) were 32 (6.2%) and 195 (42.5%) for exposed and unexposed patients, respectively. Table 1 summarizes the main characteristics of the two populations.

We found no cases of PML in the population not ex-

Table 1. Population characteristics

Parameter	Rituximab exposed (<i>n</i> = 517)	Rituximab unexposed (<i>n</i> = 459)	<i>p</i> -value
Mean age at diagnosis of non-Hodgkin's lymphoma $\pm$ standard deviation, yrs	58.3 $\pm$ 14.1	61.5 $\pm$ 14.0	<.001
Male, <i>n</i> (%)	285 (55.1)	206 (44.9)	.002
Brain imaging, <i>n</i> ^a (%)	38 (7.4%)	35 (7.6)	.903
Grade ^b (aggressive)	238 (46.0)	222 (48.4)	.480
Stage ^c (advanced)	76 (14.8)	82 (17.9)	.397
Progressive multifocal leukoencephalopathy	5	0	–
Person-years	2,083	2,147	–

^aPatients receiving at least one of the following procedures: brain computed tomography scan, magnetic resonance imaging, or neurological visit.
^bLow grade or aggressive (World Health Organization classification).
^cEarly disease (Ann Arbor stage I or stage II) or advanced disease (Ann Arbor stage III or stage IV).

posed to rituximab and five cases in the exposed population. Details of these cases were published previously [6, 7]. Four of the five cases of PML in the group exposed to rituximab were confirmed by the detection of JC virus (JCV) DNA in stereotactic brain biopsy samples (immunohistochemistry for JCV proteins was not requested at that time). The remaining case was diagnosed by MRI only, and classified as probable PML according to consensus terminology [12]. Statistically significant differences on univariate analysis were identified for gender and age. The two populations did not differ either for disease characteristics (grade of NHL and stage at diagnosis) or for the rate of patients subjected to neurology-oriented procedures. Figure 1 displays the distribution of the two populations based on the year of NHL diagnosis, and it shows that the unexposed cohort is at least in part “historical” (mean follow-up, 4.7 ± 3.4 years versus 4.0 ± 3.41 years in unexposed and exposed patients, respectively). During the observational period, the time courses of the percentage of patients receiving neurologic-oriented procedures were similar in the exposed and unexposed groups ($p = .534$) (Fig. 2). Table 2 displays the incidence rate as well as the unadjusted and adjusted RDs for PML in both patients exposed to rituximab and unexposed controls.

DISCUSSION

Rituximab was approved by the U.S. Food and Drug Administration for the treatment of NHL in 1997, and in 1998 it received marketing authorization in Europe. The inclusion of rituximab in established standard chemotherapy regimens has led to a major improvement in the survival rate for most CD20⁺ B-cell lymphomas [4], with a favorable tolerability profile. The most common adverse events

have been mild to moderate infusion-related reactions during the first administration, with the incidence markedly lower during subsequent infusions. When added to the majority of chemotherapy regimens, rituximab causes higher rates of neutropenia and hypogammaglobulinemia [4], which translate into higher infection rates [17].

In 2002, Goldberg and colleagues reported the first two cases of PML in patients with NHL receiving rituximab [18]. In February 2006, after several cases of PML were reported in patients with autoimmune diseases, labeling of rituximab was first updated to include information about PML [19]. However, the assessment of a causal relationship between PML and rituximab represents a harder challenge in NHL patients, because they bear a basal risk for the development of PML resulting from both their disease and the related immunosuppressive chemotherapies.

The statistical analysis performed in the present study suggested a higher risk for PML in NHL patients exposed to rituximab. The higher occurrence of PML can be calculated as being in the range of 0.1–4.3 for every 1,000 patient-years for NHL patients exposed to rituximab, as compared with unexposed patients. This risk is likely low enough to not overcome the benefits in terms of mortality exerted by rituximab in most NHL patients.

It must be noted that the present study could be affected by limitations, resulting in a possible overestimation of the PML risk.

First, notoriety bias, resulting from media claims after the discovery of a potential association between rituximab (and other monoclonal antibodies) and PML, might have enhanced awareness among clinicians, with a consequent increase in the request for neurologic-oriented diagnostic procedures, thus favoring the discovery of new cases, par-

Figure 1. Distribution of patients by year of first diagnosis of non-Hodgkin's lymphoma.

Figure 2. Percentage of patients receiving neurologic-oriented procedures (computed tomography scan, magnetic resonance imaging, neurologic consultations) per year ($p = .534$). (Data recorded up to April 2008.)

Table 2. Incidence rate, unadjusted RD, and adjusted RD $\times$ 1,000 person-years for progressive multifocal leukoencephalopathy in patients exposed to rituximab versus unexposed controls

Rituximab exposure	Incidence rate (95% CI)	Unadjusted RD (95% CI)	Adjusted ^a RD (95% CI)
Unexposed	0.0 (0.0–1.8)	–	–
Exposed	2.4 (1.0–5.6)	2.4 (0.3–4.5) ^b	2.2 (0.1–4.3) ^b

^aGender and age.

^bCalculated using the method described by Armitage et al. [16].

Abbreviations: CI, confidence interval; RD, rate difference.

ticularly in exposed patients. Indeed, patients in the latter cohort are distributed with higher frequencies in the recent past, compared with controls, with a higher probability of being prone to this bias. However, the lack of a significant difference in requests for neurologic-oriented procedures between the two groups as well as the similarity in the time course of the percentage of patients receiving neurologic-

oriented procedures, as shown in Figure 2, argue against the hypothesis of an influence of notoriety bias.

Second, the number of PML cases in the present analysis is small and they were recruited at a single center, thus potentially affecting the robustness of any statistical inference. Based on the rarity of PML in NHL patients, a retrospective longitudinal study of a patient population pooled

from several hematological centers would probably represent a more appropriate approach.

Third, the unexposed cohort was recruited mainly in the prerituximab era, thus leading to undisclosed confounding (such as accessibility to stereotactic brain biopsy to diagnose PML) related to the use of a control population that is, at least in part, “historical” in nature. Of note, because rituximab has proven effectiveness in NHL patients, nowadays ethical reasons prevent investigators from creating unexposed groups. As a consequence, it will be very difficult to select controls different from historical or internal ones in the future.

Fourth, we were not able to control for chemotherapy regimen, because the extreme variability in drugs, dose, and timing would have negatively affected the statistical model. However, because the distributions of NHL grade and stage at diagnosis were the same in the two populations, it seems reasonable to suppose that both populations were exposed to about the same regimens of standard chemotherapies (e.g., it is expected that patients receiving rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] matched with controls receiving CHOP in the prerituximab era). Advances in the knowledge of the safety profile of rituximab in the last decade should prompt regulatory actions after a careful reassessment of its benefit–risk balance, which seems to largely depend on the therapeutic indication for which rituximab is used. In recent times, three cases of PML in patients with psoriasis were considered sufficient to withdraw efalizumab from the world market, but the relevance of a nonlife-threatening indication (psoriasis) and poor drug effectiveness played a

major role in this extreme decision [1]. In light of this consideration, the use of rituximab for indolent autoimmune disorders and maintenance treatment in NHL patients in complete remission should be subjected to critical re-evaluation.

In conclusion, patients with NHL treated with rituximab can be regarded as the HIV[−] population carrying the highest risk for developing PML [8]. Our data suggest that rituximab exposure might significantly contribute to this risk, although some uncertainty remains because of potential uninvestigated confounding. A retrospective longitudinal study performed on patient populations pooled from several hematological centers worldwide is required in order to better clarify the role of rituximab in the development of PML in HIV[−] NHL patients. In the meantime, our study provides a reasonable estimate of this risk. Physicians should consider PML in the differential diagnosis for neurological symptoms in NHL patients previously treated with rituximab.

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Marco Tuccori and Daniele Focosi contributed equally to this manuscript.

AUTHOR CONTRIBUTIONS

Conception/Design: Daniele Focosi, Marco Tuccori
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