Late-Onset Neutropenia After Rituximab-Containing Therapy for Non-Hodgkin Lymphoma

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Abstract

The incidence of late-onset neutropenia resulting from rituximab among 183 patients with non-Hodgkin lymphoma was 6% (13 episodes in 11 patients). The median time to onset of neutropenia was 75 days, and the median duration was 100 days. Although infectious complications were uncommon, early recognition is required to avoid life-threatening complications.

Background: Late-onset neutropenia (LON) is a known adverse effect to rituximab therapy. Information about its real incidence and clinical implications comes from case reports and few retrospective studies specifically designed to study LON. However, large prospective studies of LON are lacking in the literature. We aimed to determine the incidence of LON in a group of non-Hodgkin lymphoma patients treated with rituximab and to analyze the clinical course, complications, and risk factors associated with LON. **Patients and Methods:** We retrospectively reviewed 183 patients with a diagnosis of non-Hodgkin lymphoma consecutively treated with rituximab alone or in combination with chemotherapy. **Results:** We identified 11 patients with grade 3/4 LON (13 episodes) out of 183 patients (6%). The median time to onset of LON was 75 days, and the median time to recovery from neutropenia was 100 days. The median neutrophil count nadir was 0.55 $\times$ 10^9/L (range, 0.06-0.9 $\times$ 10^9/L). Two patients presented infectious complications, one with fatal outcome. **Conclusion:** In our experience, the incidence of recognized LON is low (6%), although its real incidence may be greater because of the asymptomatic course and quick recovery in most cases. Infectious complications are unusual, but life-threatening complications can emerge. A careful evaluation of all cases of LON is warranted.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 12, 761-5
Keywords: Anticancer therapy, Anti-CD20, Chemoimmunotherapy, Haematological toxicity, Secondary effects

Introduction

The anti-CD20 monoclonal antibody rituximab is part of the standard treatment of patients with B-cell non-Hodgkin lymphoma (NHL), including follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), and small lymphocytic lymphoma/chronic lymphocytic leukemia. Other approved and off-label indications in several autoimmune diseases as well as in the setting of stem cell transplantation (SCT) are rapidly extending.[1,2]

With the increasing use of rituximab in the postmarketing setting, many adverse effects have been recognized, including, among others, late-onset neutropenia (LON).[3,4] LON is defined as an unexplained neutropenia occurring at least 4 weeks after last dose of rituximab in a patient who had recovered from previous chemotherapy-induced neutropenia. The real incidence of LON and its clinical course remains unknown because of the lack of specifically designed prospective trials. The reported incidence of LON ranges 5.3% to 27.3%, with a median time to onset of 70 to 175 days.[5-12] Furthermore, its predisposing risk factors and exact pathogenic mechanisms are also poorly understood.

Our aim was to investigate the incidence of LON in a group of patients with B-cell NHL treated with rituximab, review its clinical

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Submitted: Apr 6, 2015; Revised: Jul 27, 2015; Accepted: Jul 28, 2015; Epub: Aug 6, 2015

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.07.635

course and complications, and evaluate the risk factors associated with LON.

Patients and Methods

We retrospectively reviewed the medical records of 183 consecutive patients attended at the Department of Medical Oncology of Hospital Universitario de Gran Canaria Dr Negrin with a diagnosis of B-cell NHL who were treated with rituximab either in combination with chemotherapy or as single agent from 2003 to 2013. Patients with a minimum follow-up of 1 year were included in the study. Treatment protocols and follow-up visits were performed in a daily care setting according to standard clinical practice guidelines during the study period. As a general rule, complete blood counts were performed at every follow-up visit; 1 month after the end of therapy; every 4 months for the first 2 years; every 6 months up to the fifth year; and yearly thereafter.

LON was defined as a neutropenia grade 3 (absolute neutrophil count [ANC] of ≥ 0.5 and $< 1.0 \times 10^9$/L) or grade 4 (ANC of $< 0.5 \times 10^9$/L) according to the National Cancer Institute Common Toxicity Criteria v4.03 (2010) without an apparent cause, occurring at least 4 weeks after last dose of therapy and after ANC had previously recovered to normal.

Time to onset of LON was measured from last dose of rituximab to detection of neutropenia grade 3/4. Duration of neutropenia was measured from detection of neutropenia grade 3/4 to ANC $> 1.0 \times 10^9$/L. Occurrence of other alterations in blood cell counts, serum immunoglobulin levels, and infectious complications during LON episodes were also analyzed. The study was carried out according to the principles of the Declaration of Helsinki with its current amendments.

Statistical analyses were performed by SPSS 19.0 (IBM, Armonk, NY).

Results

We identified 11 (6%) of 183 patients fulfilling the defined criteria for LON. The main patient characteristics are outlined in Table 1.

Clinical characteristics of LON episodes (n = 13) are listed in Table 2. Interestingly, all patients developed LON after receiving a rituximab-containing regimen, with no case of LON observed among 34 patients who received rituximab as a single agent. The median time to onset of LON was 75 days (range, 30-198 days). The median time to recovery from neutropenia was 100 days (range, 21-324 days). Seven patients (63.6%) had neutropenia grade 3, and 4 patients (36.4%) had neutropenia grade 4 (rate of grade 4 LON = 2.2%). The median neutrophil count nadir was 0.55×10^9/L (range, 0.06-0.9 $\times 10^9$/L). Five patients received granulocyte colony-stimulating factor (GCSF) during LON episodes, leading to the resolution of neutropenia in all cases.

All patients presented with concomitant lymphocytopenia during LON episodes (grade 3/4 in 7 patients), with a median of absolute lymphocyte count nadir of 0.52×10^9/L (range, 0.12-1.25 $\times 10^9$/L). Additionally, 4 patients showed thrombocytopenia and 5 patients presented anemia (grade 3/4 in 1 patient each, respectively). Data about serum immunoglobulin levels were available in 8 cases of LON. All showed normal values of IgA, while 4 and 2 patients had low levels of IgG and IgM, respectively.

Table 1 Patient Characteristics

Characteristic	All Patients (n = 183)	Patients With LON (n = 11)
Age (Years)		
Median (range)	62 (28-85)	60 (37-82)
≥60	109 (59.6)	6 (54.5)
<60	74 (40.4)	5 (45.5)
Sex		
Male	83 (45.4)	5 (45.5)
Female	100 (54.6)	6 (54.5)
Histology		
DLBCL	74 (40.4)	2 (18.2)
FL	64 (35)	7 (63.6)
MZL	34 (18.6)	1 (9.1)
MCL	8 (4.4)	1 (9.1)
SLL	3 (1.6)	0
Stage		
I	46 (25.1)	0
II	35 (19.1)	1 (9.1)
III	24 (13.1)	2 (18.2)
IV	78 (42.6)	8 (72.7)
BM Involvement		
Yes	64 (35)	5 (45.5)
No	119 (65)	6 (54.5)
No. of Therapies		
Median (range)	1.42 (1-4)	1.63 (1-4)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: BM = bone marrow; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; LON = late-onset neutropenia; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; SLL = small lymphocytic lymphoma.

Bone marrow biopsies were performed in 4 patients, all of which revealed decreased cellularity; granulocytic hypoplasia with myeloid maturation arrest was found in 3 patients.

Retreatment with rituximab was attempted in 4 patients after resolution of LON, with 3 patients developing recurrent episodes of LON. Two patients developed grade 2 LON (ANC 1.0-1.5 $\times 10^9$/L) and 1 patient developed 2 episodes of grade 4 LON, the first after 45 days of rituximab retreatment (resolved in 13 days with GCSF support) and the second spontaneously after 6 months of the last rituximab dose (resolved in 120 days without GCSF therapy).

There were 2 infectious complications among 11 patients with LON (18.1%). One patient had acute bronchitis, which resolved with oral antibiotics. The other patient (refractory mantle-cell lymphoma in the fourth line of chemotherapy) died from bilateral pneumonia.

Discussion

The true incidence of LON in patients with NHL receiving rituximab therapy is not well defined. Our study shows an incidence of recognized LON of 6% among 183 patients, which is, to our knowledge, the largest series published to date. This is in line with other previously published series, which presented incidences varying from 5.3% to 27.3% (Table 3)[5-12] and is much higher than the 0.02% calculated in the postmarketing reporting rates of