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Late-Onset Hematological Toxicity (LOHT) in Patients with B-Cell Lymphomas: A Survey in 758 Cases

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ABSTRACT

Background: The increasing survival of patients with non-Hodgkin lymphoma has allowed the diagnosis of long-term complications, including late-onset hematological toxicity (LOHT), transitory cytopenias, or therapy-related myeloid neoplasm (t-MDS/t-AML). **Objective:** The objective of the study was to determine the frequency and clinical evolution of LOHT in patients with lymphoproliferative malignancies. **Materials and Methods:** Two cohorts of patients B-cell lymphomas were reviewed. Patients who achieved full hematologic recovery at the end of treatment, and thereafter developed any degree of cytopenia were included in the study. Clinical and biochemical parameters were compared between patients with and without cytopenias with X2 test. Bi- and multivariate analyses were performed to evaluate factors associated with the development of late-onset cytopenias. **Results:** Of 758 patients enrolled, 19 developed cytopenias (2.5%). Transitory cytopenia was documented in 6 cases, 3 developed ICUS, 8 t-MDS, and 2 t-AML. In patients with FL, only hemoglobin < 12 g/dL (p = 0.032) and >6 nodal areas (p = 0.037) at diagnosis were factors statistically significant for the development of cytopenia. During cytopenias, 55% of patients died. **Conclusions:** LOHT constitutes a cause of morbidity and mortality in 2.5% of lymphoma patients treated with different therapy regimens. (REV INVEST CLIN. 2021;73(2):72-8)

Key words: Transitory cytopenias. Therapy-related myeloid neoplasm (t-MDS/t-AML). B-cell lymphomas. Late-onset toxicity.

INTRODUCTION

The increase on survival rate of patients with non-Hodgkin lymphoma has allowed the diagnosis of long-term complications, including transitory cytopenias and therapy-related myeloid neoplasms (t-MN: t-MDS/t-AML)[1,2]. Progenitor stem cells are truly sensitive to damage caused by chemotherapy; there are different degrees of toxicity to the same chemotherapy schedule between populations[2-5].

The incidence of t-MN after conventional therapy ranges from 0.8%-6.3% to 20 years and may result from an impaired ability to detoxify chemotherapeutic drugs or repair drug-induced genetic damage caused by genetic polymorphisms in enzymes involved in the

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metabolism of drugs[1]. t-MDS/t-AML are an evident cause of long-term, non-relapse mortality[5,6].

Rituximab is a monoclonal antibody widely used for the treatment of different B-cell neoplasms, and even though it has not been associated with acute myelosuppression[7], late-onset cytopenias (LOC), such as neutropenia, has been described with a post-commercialization rate of 0.02% in more than 30,000 patients, but according to different publications, this rate is higher. A single study has also described neutropenia in 9% of patients and a decrease of up to 30% from the baseline platelets[8]. Most of LOC are self-limited and have a spontaneous regression. However, they also may have an impact on long-term survival, since according to their severity, patients may have a higher risk of infections and may require transfusion of blood-derived products. To determine the frequency and clinical evolution of LOHT in patients with lymphoproliferative malignancies, two cohorts of patients with follicular and diffuse large B cell lymphomas were reviewed.

MATERIALS AND METHODS

Two cohorts of patients B-cell lymphomas attending from January 2011 to December 2015 at the Instituto Nacional de Cancerología México were reviewed. Late-onset hematological toxicity was defined as any cytopenia, developed after complete hematological response lasting at least 2 months, and was classified in three groups: (1) late-onset transitory cytopenia (LOC) defined as any self-limited cytopenia (1), (2) idiopathic cytopenia of unknown significance (ICUS) defined as peripheral cytopenia, not self-limited, not fulfilling MDS criteria, no MDS-related mutation[9], and (3) therapy related-myeloid neoplasms (t-MN) were defined as patients who develop t-MDS/t-AML myelodysplasia (t-MDS) or acute leukemia (t-AML) after exposure to cytotoxic or radiation therapy for an unrelated malignancy[2].

Inclusion criteria

Age ≥18 years, diagnosis of either follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL), treated with rituximab based schemas, achievement of complete hematologic recovery at the end of treatment[10], and thereafter, developed any degree of cytopenia. We excluded patients with HIV or other infections, hepatopathy, uncontrolled thyroid disease, active immune diseases, any active neoplasm, or other hematologic diseases or recent exposition to myelotoxic. In all patients, peripheral blood smear and bone marrow examination with cytogenetic analysis were performed. Cytopenias were defined according with CTCAE v.4 criteria[10] as: neutropenia as neutrophils < 1500/mm^3, anemia as hemoglobin < 11.0g/dL, and thrombocytopenia as platelets < 100,000 mm^3.

Clinical parameters

That was analyzed included sex, age, B-symptoms, Eastern Cooperative Oncology Group (ECOG) performance status[11], clinical-stage by Lugano classification[12], the presence of bone marrow infiltration, bulky disease, number of nodal sites at diagnosis, International Prognostic Index (IPI score) for DLBCL, Follicular Lymphoma International Prognostic Index (FLIPI score) for FL, date of diagnosis, response to treatment[12], date of relapse, date of mortality, and last hospital visit. Baseline levels biochemical parameters analyzed included: lactic dehydrogenase (LDH), β2 microglobulin (β2mcg), serum albumin, hemoglobin, absolute leukocyte, neutrophil, and lymphocyte counts.

Treatment protocols for DLBCL included the following[13-15]

RCHOP (375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, 1.4 mg/m^2 vincristine [maximal total dose: 2 mg], and 100 mg/day/5 days prednisone), DA-EPOCH-R (375 mg/m^2 rituximab; 50 mg/m^2 etoposide, daily in 96 h continuous infusion; 10 mg/m^2 doxorubicin, daily in 96 h continuous infusion; 0.4 mg/m^2 vincristine, daily in 96 h continuous infusion; and 750 mg/m^2 cyclophosphamide, on day 5), R-CVP (375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide, 1.4 mg/m^2 vincristine [maximal total dose: 2 mg], and 100 mg/day/5 days prednisone), R-high dose methotrexate (375 mg/m^2 rituximab and methotrexate 1-3 g/m^2), and R-ICE (375 mg/m^2 rituximab, 5g/m^2 ifosfamide on day 4, carboplatin AUC = 5 on day 4, and 100 mg/m^2 etoposide on day 3-5).

Treatment schemas for follicular lymphoma included

R-bendamustine (375 mg/m^2 rituximab and 90 mg/m^2 bendamustine on days 1-2), FCR (375 mg/m^2 rituximab, 25 mg/m^2 fludarabine on days 2-4, and 250 mg/m^2 cyclophosphamide on days 2-4), R-ESHAP (375 mg/m^2 rituximab, 40mg/m^2 etoposide on day 1-4, 25 mg/m^2 cisplatin on day 1-4, and 2 g/m^2 cytarabine on day 5), and RCHOP, as previously described. The addition of radiotherapy (dose and site) was given according to clinical indication.

The response to treatment was evaluated using standard international criteria. For patients in whom PET/CT was performed before and after treatment, Deauville criteria were used (12). In cases with increased blood glucose levels (>170 mg/dL), which contraindicated the performance of PET/CT, only a CT was performed, and the response was evaluated by standard Cheson criteria[12].

Ethical aspects

This is a retrospective study. The review of clinical files had the corresponding IRB approval (REV 003/19).

Statistical analysis

Baseline descriptive analysis was performed; including quantitative and qualitative variables were done; clinical and biochemical parameters were compared between patients with and without cytopenias with X^2 test. Bi- and multivariate analyses were performed to evaluate factors associated with the development of late-onset cytopenias. Factors analyzed included: gender, B symptoms, bulky disease, clinical stage, number of nodal sites at diagnosis, ECOG score, bone marrow infiltration, and biochemical parameters (increased LDH, increased β2-microglobulin, hemoglobin, albumin, leukocytes, neutrophil, and lymphocytes values), (IPI score) for DLBCL, and (FLIPI score) for FL. Odds ratios (OR) and their respective 95% confidence interval (CI) were calculated to identify associations. Overall survival (OS) was calculated using the Kaplan–Meier method. Cumulative incidence was also calculated for t-MDS and t-AML. Statistical analysis was performed using SPSS (version 20; IBM Corp., Armonk, NY, USA).

RESULTS

From January 2011 to December 2015, 840 patients (695 with DLBCL and 145 with FL attended at this Institution). Of them, 758 (626 DLBL and 132 FL) were included in this analysis. No difference within clinical or biochemical values was found between the patients with or without LOHT. In the whole group, 60% received chemotherapy and radiotherapy and 33.4% received only chemotherapy. No difference within treatment intensity was documented between patients with and without LOHT.

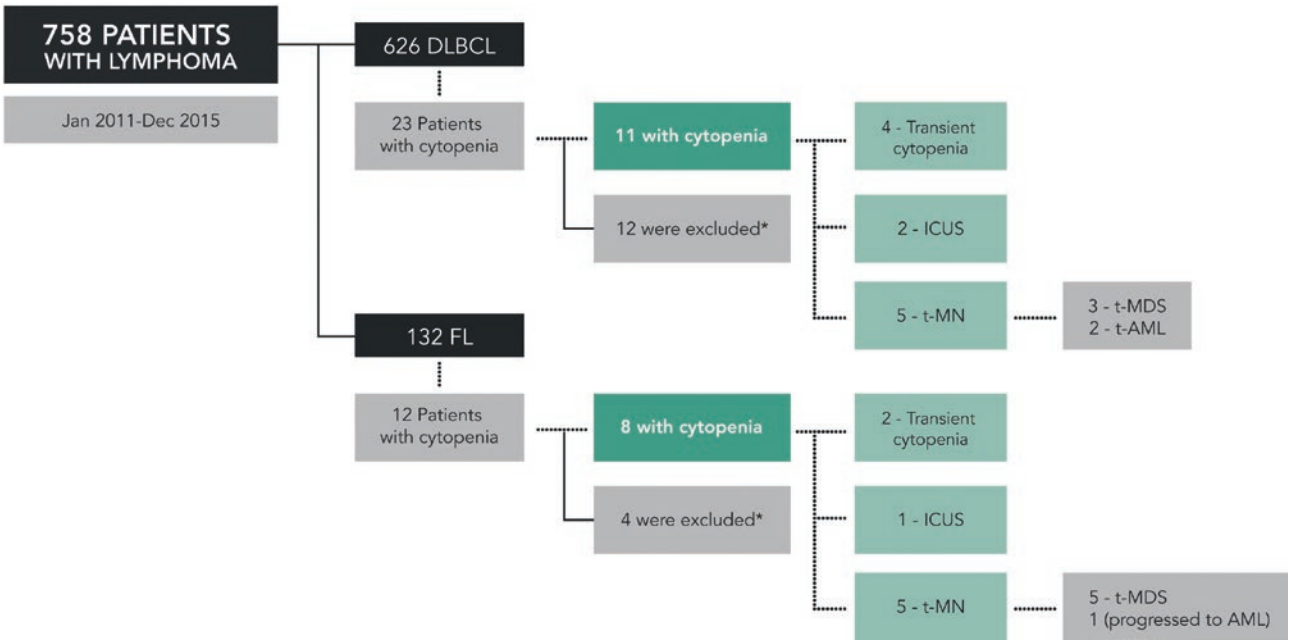
During a mean follow-up of 54 months, as detailed in Figure 1, 19 patients developed LOHT (2.5%) (11 with DLBCL and 8 with FL). The most frequent cytopenia was neutropenia in DLBCL (n = 3, 27.2%) and pancytopenia in FIL (n = 4, 50%). Seven patients (36.8%) were hospitalized because of febrile neutropenia (1 with transitory cytopenia and 6 with t-MN); 3 patients required transfusion: 1 patient with t-MN required platelet transfusion (9.7 units); and 2 patients with t-MN required red blood cells (RBC) (mean 5 units). During cytopenia 11 patients died (57.9%); the causes were: t-AML (n = 4, 21%), t-MDS (n = 4, 21%), and fever and neutropenia (n = 3, 15.7%); no patients in the group of transitory cytopenia died. For those patients with transitory cytopenias, median time to the presentation of cytopenia was 24.5 months since the last chemotherapy with a median time to recovery of 6 months. Meantime to presentation for patients with t-MDS (after last chemotherapy) was 8.5 months, and for patients with t-AML mean time to presentation was 21 months.

Evolution of LOHT

Of the 19 patients with cytopenias, ten patients developed therapy related-myeloid neoplasms (t-MN): 8 t-MDS and 2 t-AML. The detailed clinical evolution of these cases is shown in Table 1. Both patients who developed t-AML (patients 1 and 2 died after 7 and 8 months due to infections and bleeding, respectively. Five patients with t-MDS also died and the rest of patients with t-MDS remain alive to a mean follow-up of 10.2 months (range: 4-29).

Three patients with FL relapsed after 10, 12, and 25 months of the development of LOC; at relapse, these patients had already recovered from cytopenias.

Figure 1. Distribution of cytopenias in patients with diffuse large B cell lymphoma and follicular lymphoma. *We excluded developed cytopenias due to vitamin deficiencies, bone marrow hypoplasia, thyroid disease, hypersplenism, among other peripheral causes of cytopenias. DLBCL (diffuse large B cell lymphoma), FL (follicular lymphoma), ICUS (idiopathic cytopenia of undetermined significance), t-MN (therapy-related myeloid neoplasms), t-MDS (therapy-related myelodysplastic syndrome), t-AML (therapy-related acute myeloid leukemia).



Risk factors to develop LOHT

After bivariate analysis, only hemoglobin <12 g/dL (OR: 3.59, [95% confidence interval: 10.93-15.35]) (p = 0.032) and ≥ 6 nodal sites (p = 0.037) (OR: 7.01, 95 % confidence interval: 5.72-15-19) at diagnosis were associated with LOHT in patients with follicular lymphoma. After multivariate analysis, no risk factor was associated with the presence of cytopenias. In FL, the presence of LOHT was associated with an increased rate of relapse: 54.5% versus 13.6% in patients without cytopenias (p = 0.002). In patients with DLBCL, the development of LOHT was not associated with an increase of relapse rate.

Survival

As shown in Figure 2, mean overall survival (OS) has not been achieved at 60 months in patients with LOHT. In the group of patients with t-MDS, mean OS has neither been achieved and was similar to those patients with ICUS or transitory cytopenia. However, the median OS was 5.2 months in patients with t-AML. Therefore, the development of transitory cytopenia, ICUS, or t-MDS has a negative impact on overall survival.

DISCUSSION

Hematopoietic stem cells are particularly sensible to chemotherapy and there is also a wide grade of response in terms of toxicity between patients[7]. Since the last decade, with the increasing use of rituximab as monotherapy or as part of different chemotherapy schedules, there is an increased survival in patients with B cell lymphomas and there are still many questions about the late adverse effects of this antibody. Late-onset neutropenia was initially described to be asymptomatic in patients treated with rituximab, but in our group of patients, there is a high incidence of infections (22.8%) requiring hospitalization, which also increases morbidity and health costs[16-17].

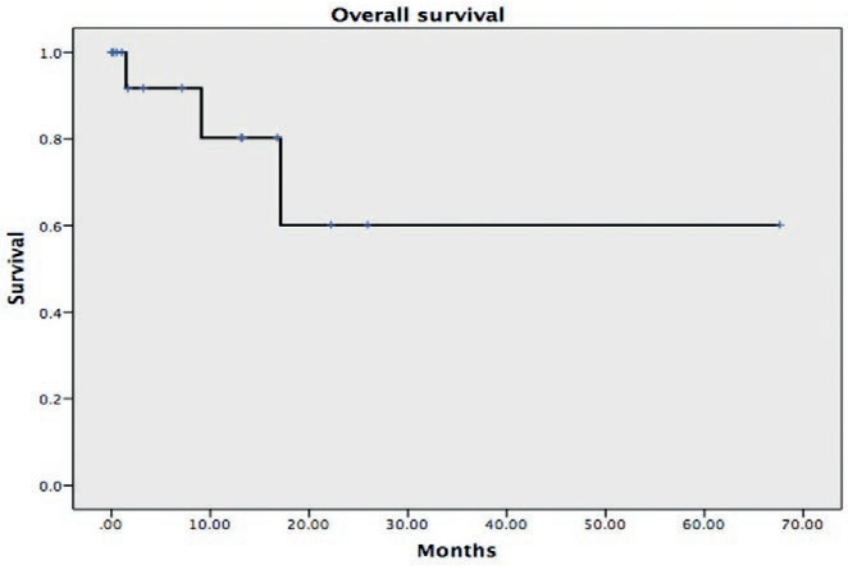
According to different studies[16-21], the following risk factors have been associated as risk factors for cytopenias: age, gender, lymphoma subtype, bone marrow infiltration, hypogammaglobulinemia, previous

Table 1. Patients with t-MN described individually

Patient	1[a]	2[a]	3[a]	4[a]	5[a]	6[b]	7[b]	8[b]	9[b]	10[b]
Age at diagnosis of lymphoma	83	59	58	70	63	62	61	68	62	51
1st line therapy: R-CHOP (number of cycles)	6	8	4	6	6	7	8	8	8	8
2nd line therapy	–	–	–	–	–	FCR	FCR	R-Mitoxantrone	Rituximab	FCR
Number of chemotherapy lines	1	1	1	1	1	2	3	2	5	2
Radiotherapy	30 Gys	30 Gys	No	No	36 Gys	30 Gys	36 Gys	30 Gys	24 Gys	30 Gys
Months between full hematologic recovery and event	20	25	15	7	2	15	1	11	14	2
t-MDS subtype	–	–	MDS-MLD	MDS-MLD	MDS-MLD	MDS-MLD	MDS-MLD	MDS-MLD	MDS-MLD	MDS-MLD
MDACC risk model score	–	–	Intermediate	Good	Intermediate	Intermediate	Intermediate	Poor	Intermediate	Poor
Karyotype	Complex karyotype	NA	(-7,-13)	Normal	Complex karyotype	Complex karyotype	NA	Normal	92,XXXX[8]/ 46,XX[10]	47xx +11
t-AML subtype	M0	M4 E0	–	–	–	–	–	–	–	–
Therapy	Cytarabine	Cytarabine	Support	Danazol	G-CSF	G-CSF	Support	Azacitidine	Azacitidine	Support
Response to therapy	NR	NR	NR	HI	HI	HI	HI	NA	Failure	Progression t-AML M6
Actual status/ months since t-MN diagnosis	Dead/ 7 months	Dead/ 8 months	Dead/ 1 month	Alive/ 11 months	Alive/ 4 months	Alive/ 4 months	Alive/ 29 months	Dead/ 3 months	Dead/ 3 months	Dead/11 months

[a]DLBCL: diffuse large B cell lymphoma; [b]FL: follicular lymphoma; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; FCR: fludarabine, cyclophosphamide, rituximab; Gys: unit used to measure the total about of radiation the patient is exposed to; t-MDS: therapy-related myelodysplastic syndrome; MDS–MLD: myelodysplastic syndrome with multilineage dysplasia; MDACC: The University of Texas M. D. Anderson Cancer Center risk model; NA: not available; t-AML: therapy-related acute myeloid leukemia; M0: minimally differentiated AML; M4EO: myelomonocytic leukemia with eosinophilia; G-CSF: granulocyte colony-stimulating factor; NR: no response; HI: hematologic improvement; t-AML M6: erythroleukemia; t-MN: therapy-related myeloid neoplasms.

Figure 2. Overall survival in patients with diffuse large B cell lymphoma and follicular lymphoma with late-onset cytopenias.



chemotherapy, bone marrow transplant, previous exposition to fludarabine, and time of exposition to rituximab[22].

Transitory thrombocytopenia has been identified by Wilop et al.[23], in a cohort of patients with DLBCL, found in up to 7.2% of the patients with a 30% reduction of platelet baseline count, either when rituximab was given as a single agent or in combination with chemotherapy. No prospective studies have defined it as a long term complication as late-onset neutropenia (LON)[24-26]. In our series, 1 patient with transitory cytopenia required hospitalization due to fever and neutropenia and recovery was documented 1 month later, with no further evidence of new events during follow-up. Fever and neutropenia by itself demonstrate the negative impact of this late-onset complication.

In the literature, other morphologic alterations have been associated with LON, particularly, 4 cases have been described with arrest in differentiation, remaining as promyelocytes, without the presence of large granular lymphocytes, and we were able to identify a patient with this particular morphologic feature (Table 1)[26].

Previous studies[19-21,25,26] reported lower rates of prolonged cytopenias than the ones in our study, probably associated with different characteristics of the populations and that ours is a retrospective cohort, so we propose a further prospective study with close monitorization.

t-MDS was the most common cause of cytopenia in patients with follicular lymphoma, probably associated with multiple line treatments according to more frequent relapses in this particular group of patients. Since fludarabine is suggested as a second-line treatment in this lymphoma, we consider the need of the development of a biomarker able to predict the bone marrow toxicity associated with chemotherapy[22,27]. In the past years, some conditions have been defined as pre-MDS, or ICUS[14], and even though it has not been studied in patients exposed to chemotherapy, we found that ICUS represented 15.7% for both lymphomas and this particular group of patients need closer follow-up because progression to t-MN is still unknown. In our series, these cases were followed during 3, 5, and 16 months without achieving criteria to be classified as t-MDS or t-AML. Interestingly, only two patients with t-AML have previous DLBCL, apparently without previous myelodysplasia and only one previous line-treatment but were exposed to radiotherapy without other risk factors identified.

Patients with t-MDS do not have a good response to treatment, with overall survival of 62.5% at 30 months;

still, the only available prognostic scale for this t-MN needs to be validated in our population to personalize treatment and for evaluation of response.

In conclusion, sample was too small to identify any statistically significant risk factors associated with the development of t-MN. There is no other study of this kind in our country, so these preliminary results could be the precedent for the creation of a cooperative group for the development of a prospective study to identify the role of late cytopenias in therapy-related myeloid neoplasm (t-MN). We aim for the early identification of patients at risk and the personalization of treatment in patients with t-MN.

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