EUR. J. ONCOL.; Vol. 20, n. 1, pp. 64-67, 2015

Drug-related side effects after rituximab infusion in patients with chronic lymphocytic leukemia

Giovanni D'Arena[1], Sonya De Lorenzo[2], Maria Luigia Vigliotti[3], Idanna Innocenti[4], Michele Cimminiello[5], Vittorio Simeon[6], Francesco Autore[4], Giuliana Farina[3], Vincenzo Patella[7], Vincenzo De Feo[8], Pellegrino Musto[9], Luca Laurenti[4]

[1] Hematology and Stem Cell Transplantation Unit, IRCCS Referral Cancer Center of Basilicata, Rionero in Vulture (PZ), Italy; [2] Hematology Unit, "A. Tortora" Hospital, Pagani (SA), Italy; [3] Hematology Unit, "San Sebastiano" Hospital, Caserta, Italy; [4] Hematology Unit, Catholic University of "Sacro Cuore", Rome, Italy; [5] Hematology Unit, "S. Carlo" Hospital, Potenza, Italy; [6] Laboratory of Preclinical and Translational Research, IRCCS Referral Cancer Center of Basilicata, Rionero in Vulture (PZ), Italy; [7] Allergology Unit, "Santa Maria della Speranza" Hospital, Battipaglia (SA), Italy; [8] Department of Pharmacology, University of Salerno, Italy; [9] Scientific Direction, IRCCS Referral Cancer Center of Basilicata, Rionero in Vulture (PZ), Italy

A great advance in the treatment of all CD20 positive B-cell lymphoproliferative disorders has been achieved by the addition of anti-CD20 monoclonal antibody Rituximab to standard chemotherapy. As a consequence, Rituximab has also greatly expanded the treatment options for patients with chronic lymphocytic leukemia (CLL), a "mature" B-cell malignancy characterized by an increase in marrow and circulating neoplastic B-lymphocytes. Interestingly, several autoimmune disorders are also successfully treated with Rituximab.

Despite usually being well tolerated, the infusion of this monoclonal antibody may be complicated by side effects, most of which occur during the first administration and, at least in some reports, in patients with high tumor load (1, 2). In particular, a "cytokine-release syndrome" has been previously described and considered to be correlated to the circulating lymphocyte count in patients with CLL (1, 3). The syndrome results from the release of cytokines from cells targeted and destroyed by the monoclonal antibody; it is characterized by systemic symptoms, such as hypotension, tachycardia, fever, nausea, chills, asthenia, headache, rash and dyspnea. These symptoms may be mild to moderate in severity and are, generally, easily managed. However, other severe adverse events (SAE) may also occur, following which the drug sometimes needs to be definitively stopped.

Norin *et al.* have very recently reported data from a Swedish national observational study focusing on SAE occurring in patients with CLL undergoing Rituximab treatment (4). These authors evaluated 96 patients and found that 58% of them experienced at least one adverse drug reaction (ADR) during the first cycle. Only 5 patients (5%), however, reported grade ≥ 3 ADRs, with one grade 4 reaction. Notably, only 2 patients with ADR had a leukocyte count > 50 x 10^9/L and no correlation between leukocyte count and ADR grade was therefore found.

From October, 2014, we are conducting a retrospective study aiming to evaluate the incidence of side effects in patients treated with Rituximab for their hematologic malignancy or autoimmune disorder in the last 5 years and in 5 Italian hematologic Institutions. To date, 130 patients have been evaluated: 60 with CLL, 34 with diffuse large B-cell lymphomas, 33 with other types of B-cell lymphomas, 1 with Hodgkin's lymphomas with a lymphocyte predominance, and 2 with autoimmune disorders (1 immune thrombocytopenia and 1 acquired hemophilia A). Prompted by the data reported by Norin *et al.* (4), we focused on the ADRs occurring in CLL patients evaluated so far, reporting our preliminary data here.

The 60 patients with immunologically typical CLL were investigated (40 were male and 20 female; mean age was 66,4 years, range 46-86). According

Table 1. ADRs in CLL patients treated with rituximab, according to clinical variables.

Variables	ADRs n (%)			*p*
	All, n. 60	No, 37 (62)	Yes, 23 (38)	
Sex, n (%)				
M	40 (67)	23 (62)	17 (74)	
F	20 (33)	14 (38)	6 (26)	*0.35*
Age				
mean ± sd	66.6 ± 9.6	67.1 ± 9.4	65.9 ± 10.06	
median (range)	68.5 (46 - 86)	69 (46 - 80)	68 (47 - 86)	*0.6*
AEA, n (%)				
no	55 (92)	33 (89)	22 (96)	
yes	5 (8)	4 (11)	1 (4)	*0.38*
Rai stage, n (%)				
I	1 (2)	0	1 (4)	
II	29 (48)	14 (38)	15 (65)	
III	17 (28)	13 (35)	4 (17)	
IV	13 (22)	10 (27)	3 (13)	*0.083*
Splenomegaly (cm)*				
mean ± sd	2.78 ± 2.6	2.86 ± 2.7	2.65 ± 2.5	
median (range)	2 (0 - 10)	2 (0 - 10)	2 (0 - 9)	*0.77*
Adenopathy, n (%)				
no	5 (8)	5 (13)	0	
yes	55 (92)	32 (86)	23 (100)	*0.066*
BM infiltration (%)				
mean ± sd	74.3 ± 17.2	70.8 ± 18.9	80 ± 12.37	
median (range)	80 (20 - 95)	75 (20 - 95)	81 (50 - 95)	***0.03***
Rituximab Therapy, n (%)				
after I cycle CHT	41 (68)	30 (81)	11 (48)	
concomitant CHT	19 (32)	7 (19)	12 (52)	***0.007***
Combined chemotherapy given, n (%)				
R-F	29 (47)	22 (60)	6 (26)	
R-FC	3 (5)	1 (3)	2 (9)	
R-Chl	17 (28)	7 (19)	10 (43)	
R-B	1 (2)	1 (3)	0	
R-COP	5 (8)	3 (8)	2 (9)	
R-P	2 (3)	0	2 (9)	
R alone	4 (7)	3 (8)	1 (4)	***0.072***
Hb (g/L)				
mean ± sd	11.94 ± 2.6	11.3 ± 2.7	12.9 ± 2.01	
median (range)	12.4 (4.5 - 16.5)	11.7 (4.5 - 16)	13.3 (7.7 - 16.5)	***0.02***
Clonal B-cell lymphocytes (x10^9/L)				
mean ± sd	43.2 ± 36.4	49.7 ± 37.4	32.6 ± 32.8	
median (range)	32.8 (5.1 - 136.4)	37.1 (5.9 - 136.4)	15.4 (5.1 -112.6)	***0.032***
Platelets (x10^9/L)				
mean ± sd	152 ± 79	154 ± 84	149 ± 72	
median (range)	140 (9 - 471)	130 (50 - 471)	151 (9 - 259)	*0.7*

Legend: AEA: autoimmune hemolytic anemia; BM: bone marrow; R: rituximab; F: fludarabine; FC: fludarabine plus cyclophosphamide; Chl: chlorambucil; B: bendamustine; COP: cyclophosphamide, oncovin, prednisone; P: methylprednisolone; Hb: hemoglobin
* spleen was evaluated as cm below the left costal margin

to the Rai staging system, 1 patient was in stage 1, 29 patients were in stage 2, 17 in stage 3, and 13 in stage 4. Rituximab was given intravenously as first-line treatment and variously combined with different drugs, the most used being fludarabine, cyclophosphamide, chlorambucil and bendamustine. As shown in table 1, 23 patients (38%) experienced an ADR during the first infusion of rituximab, while 37 patients (62%) did not. Overall, 13 patients (57%) had grade 1, 7 (30%) grade 2, 1 (4%) grade 3, and 2 (9%) grade 4 ADRs, according to the Common Terminology Criteria for Adverse Events (CTCAE) (5). No correlation was found with age, gender, concomitant presence of an autoimmune hemolytic anemia, spleen and lymph node involvement, or platelet count (Table 1). The type of associated chemotherapy again did not affect ADR occurrence. On the contrary, the degree of bone marrow infiltration and the concomitant infusion of Rituximab plus chemotherapy due to delayed administration of the monoclonal antibody (generally one week after the first cycle with other cytostatic drugs) were significantly associated with a higher incidence of ADRs. Quite surprisingly, patients with more elevated hemoglobin levels and those with lower peripheral lymphocyte counts also displayed a greater risk of developing ADRs (Table 1); these patients also showed more severe ADRs (Fig. 1).

CD38 expression, IgVH mutational status and adverse cytogenetic aberrations, such as del17p and del11q, were detected only in a minority of patients and, for that reason, they were not evaluated in the present analysis (data not shown).

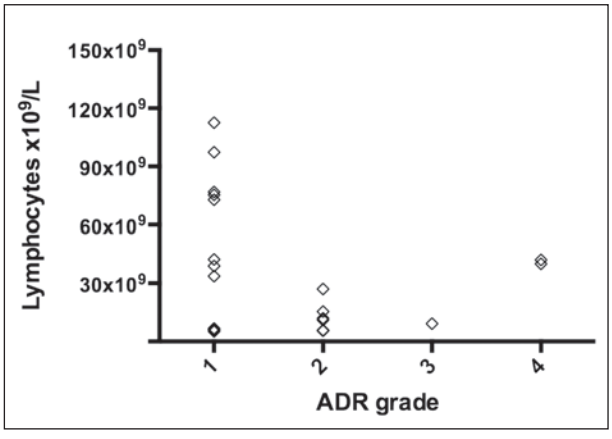

Figure 1. Correlation between lymphocytes (/μL) and ADRs grade.

Most side effects were easily managed. In the majority of cases Rituximab was temporarily stopped, while steroids and anti-histaminic drugs were given. The monoclonal antibody was then safely re-started with a less rapid infusion. Only one patient definitively stopped Rituximab treatment, due to grade 4 ADR (shock and dyspnea).

In general, in this multicenter experience, ADRs after Rituximab were commonly seen in CLL patients during the first infusion. However, they were mostly limited to grade 1 and 2 (mild-moderate) and, generally, did not provoke clinically significant effects. Indeed, Rituximab was generally re-administered during the same course of treatment. Only very few patients experienced severe infusion-related ADRs and the monoclonal antibody rarely had to be stopped definitively.

Although caution is still required, our study suggests that Rituximab, at the present time, should be given whatever the clinico-biological features of CLL patients; the first administration, however, should preferably be delayed after a first cycle of chemotherapy, to reduce the possibility of ADRs. However, certain clinico-biological variables, including pharmacogenomic parameters could be useful in predicting the development of infusional side-effects, enabling us to identify patients at higher risk for ADR and to develop appropriate preventing therapies. In light of this, we are awaiting some further answers from our ongoing study, when a greater number of patients have been evaluated.

References

1. Winkler U, Jensen M, Manzke O, *et al*. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (Rituximab, IDEC-C2B8). Blood 1999; 94 (2): 2217-24.
2. Kimby E. Tolerability and safety of rituximab (MabThera®). Canc Treat Rev 2005; 31 (6): 456-73.
3 Byrd JC, Waselenko JK, Maneatis TJ, *et al*. Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: association with increased infusion-related side effects and rapid blood tumor clearance. J Clin Oncol 1999; 17 (3): 791-5.

4 Norin S, Björkstrand B, Rommel F, *et al*. Severe infusion-related reactions are uncommon in rituximab-treated CLL patients in clinical practice: results from a Swedish national observational study. Leuk Res 2015; 39 (1): 33-7.
5 U.S. Department of Health and Human Services. National Institutes of Health, National Cancer Institute. Common terminology criteria for adverse events (CTCAE). V4.02. Published: May 28,2009. Available at http://evs.nci.nih.gov/ftp1/CTCAE/(accessed November 2, 2012).

Received: 28.11.2014
Accepted: 26.2.2015
Address: Giovanni D'Arena, MD
Hematology and Stem Cell Transplantation Unit,
IRCCS Referral Cancer Center of Basilicata,
Via Padre Pio n. 1, 85028 Rionero in Vulture (PZ), Italy
Tel. +39.0972.726225
Fax +39.0972.726217
E-mail: giovannidarena@libero.it