The frequency of detecting anti-drug antibodies in non-Hodgkin's lymphoma

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Abstract. Therapeutic antibodies are known could occasionally elicit an antibody response in patients, which can result in loss of response or adverse effects. But sometimes these antibodies are found in pre-treatment serum samples, The purpose of this study was to determine the incidence of anti-drug antibodies (ADA) in patients with non-Hodgkin's lymphoma (nHL). Serum levels of anti-rituximab antibodies was determined in blood samples of patients with nHL (newly diagnosed and resistant / recurrent forms, previously treated by rituximab) and healthy controls. Results: none of the patients with newly diagnosed disease have antibodies to rituximab. Positive results were recorded in 7 (33%) patients who received rituximab earlier and 2 healthy controls.

Keywords: rituximab, anti-drug antibodies, non-Hodgkin's lymphoma

Introduction

Monoclonal therapeutic antibodies are widely used to treat lymphoproliferative and rheumatologic disorders [1,2]. Because of their higher target specificity, monoclonal antibodies treatments are generally considered to pose a lower risk of adverse reactions than chemical drugs [3]. Rituximab, a chimeric monoclonal antibody targeted against the pan-B-cell marker CD20, was the first monoclonal antibody to be approved for therapeutic use [2]. It is usually used in combination with chemotherapy. Treatment with rituximab at standard weekly dosing is effective in more than 50% of patients with relapsed or refractory CD20-positive follicular non-Hodgkin's lymphoma, but is not curative. It is less effective in other subtypes of CD20-positive lymphoma and for retreatment, even with CD20 still expressed [4]. Thus, binding of rituximab to CD20 is not sufficient to kill many lymphoma cells, indicating that there are mechanisms of resistance.

There are quite a lot of data in the literature that therapeutic antibodies occasionally elicit an antibody response in patients, which can result in loss of response or adverse effects [5-8]. However, antibodies that bind a drug are sometimes found in pre-treatment serum samples, with the amount depending on drug, assay, and patient population. The accurate prediction and assessment of (clinically relevant) immunogenicity remains a challenging endeavor [5].

Purpose of the study - to determine the incidence of anti-drug antibodies (ADA) in patients with non-Hodgkin's lymphoma (nHL) treated by rituximab.

Materials and methods

The study involved 32 patients with nHL (11 newly diagnosed, 21 - resistant / recurrent form), aged from 36 to 70 years (average age 49,5 years), of witch 18 women and 14 men and and 13 practically healthy individuals, matched by age and sex.

In 55% of patients, stage 2 of the disease was detected, in 45% of patients - stages 3 and 4. Patients with refractory / relapsing forms have previously received 4-6 courses of R-FC therapy. Determination of anti-rituximab antibodies in peripheral blood serum was performed by enzyme-linked immunoassay using a test system manufactured by Bender Medsystems (Austria) (semi-quantitative analysis).

Results and discussion

The data are shown in the table below.

Table 1. The presence of antibodies to rituximab in the blood serum of patients with nHL and healthy controls.

Group	Result (conventional unit) *
Newly diagnosed nHL (n=11)	1.4
	0,65
	1,74
	1,1
	1,3
	1,54
	1,2
	1,53
	2,12
	1,33
	1,59
Resistant/recurrent nHL (n=21)	2,32
	2,78
	2,6
	2,8
	10,7
	1,3
	1,14
	127
	74,6
	2,4
	2,27

	9,7
	6,0
	9,3
	6,9
	1,16
	0,95
	1,43
	1,15
	0,79
	0,88
Controls (n=13)	1,77
	3.4
	0,95
	0,94
	0,81
	1,13
	0,59
	2,22
	5,18
	0,86
	1,72
	1,0
	0,77

*Note: positive results are shown in bold

As follows from the table, none of the patients with newly diagnosed disease have antibodies to rituximab. Positive results were recorded in 7 (33%) patients who received rituximab earlier. Of particular note is a patient with a very high antibody level (74,7 c.u.) who received 6 courses of combination therapy and showed pronounced progression of the disease. At the same, in the group of practically healthy persons, positive results were obtained in 2 (15,4%) cases, in particuilar, with a procedural nurse who regularly contacts the drug.

Conclusion.

Most recombinant engineered therapeutic proteins are administered to patients as repeated doses, over their lifetime. Generation of ADA is a potential outcome to almost all such therapeutics. The results of the study demonstrated that ADA are revealed in 1/3 patients with resistant forms of the disease treated by rituximab. Moreover, pre-existing ADA were detected in several healthy controls. Of course, it should be borne in mind that the effect of ADA on the therapeutic efficacy of the drug can be different: it could be

targeting predominantly the idiotype and thus clinically relevant, or due to pre-dose antibodies that can bind the therapeutic antibody, but are often irrelevant. If we suppose that immunogenicity is an important factor that should be considered in the overall treatment strategy, we should take actions to reduce antidrug antibodies formation: modifying drug administration; increasing dose; decreasing immunogenicity by adding immunosuppressive agents to the regimen or using new drugs which are supposed to be less immunogenic such as humanized or fully human monoclonal antibodies.

References

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