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RESPONSE TO SEQUENTIAL TREATMENT WITH LYMPHOBLASTOID INTERFERON-α IN PATIENTS WITH Ph+ CHRONIC MYELOID LEUKEMIA UNRESPONSIVE TO RECOMBINANT INTERFERON-α (rIFNα2a) AND NEUTRALIZING-rIFNα2a ANTIBODIES NEGATIVE

DOMENICO RUSSO, ANNA CANDONI, ROBERTA GRATTONI, ROSALBA MINISINI,* GIANANTONIO ROSTI°
*Chair of Hematology and *Chair of Microbiology Department of Clinical and Morphologic Research, Udine University, Department of Bone Marrow Transplantation, University Hospital, Udine; °Institute of Hematology and Oncology "Seràgnoli", Bologna, Italy*

ABSTRACT

Nine Ph+ CML patients in chronic phase who were hematologically and/or karyotypically unresponsive to recombinant-IFNα2a (rIFNα2a) and neutralizing-rIFNα2a Abs negative were shifted from rIFNα2a to lymphoblastoid-IFNα (IFNα-Ly) therapy. After 3 months of IFNa-Ly treatment, the hematologic response was reinduced in 3 out of the 6 pts who were resistant to previous rIFNα2a therapy, and was maintained in 2 out of 3 patients who were hematologically but not karyotypically responsive to rIFNα2a. After 6 and 12 months, the hematologic response was progressively lost, being present only in 3 out of 7 and in 2 out of 3 evaluable patients respectively. None of the hematologically responsive patients achieved a karyotypic response (Ph neg. metaphases = 0%). One patient, who was hematologically responsive, continued being treated with IFNα-ly for 36 months but he did not achieve any karyotypic response. The results of this study suggest that in the unresponsive and neutralizing-rIFNα2a Abs negative CML patients a change in therapy, by using a non cross-reactive type of IFNα, would not be advantageous.

Interferon-α (IFNα), as a single agent, is now considered as the standard treatment for Philadelphia-positive chronic myeloid leukemia (Ph+ CML). Several studies have shown that IFNα can induce hematologic responses in 60-80% of CML patients and can prolong significantly the length of chronic phase and survival in the patients who achieve and maintain not only a hematologic response,[1] but above all a karyotypic response.[2-5] However about 30% of patients never respond to IFNa and about 60% of cases do not achieve a karyotypic response. Furthermore, a substantial proportion of hematologically and karyotypically responsive patients lose the response with time. The mechanisms that are responsible for the sensitivity or resistance to IFNα are still poorly understood. Some observations suggest that the induction of neutralizing antibodies directed against IFNα (neutralizing-IFNα Abs) can be one of the reasons for resistance to IFNα. Data currently available show that: i) about 20% of the CML patients chronically treated with recombinant IFNα2a (rIFNα2a) or rIFNα2b may develop neutralizing-rIFNa Abs;[6-10] ii) the development of these antibodies is associated with the loss of IFNα efficacy;[9,10] iii) for resistant CML patients who have developed neutralizing-rIFNα2a Abs, a change in therapy by using a non cross-reactive type of IFNα, such as lymphoblastoid-IFNα one, would be advantageous for reinducing a hematological response but not a karyotypic response.[10] Based on these observations it appears that the lack of IFNα efficacy can frequently be associated with the development of neutralizing-IFNα Abs, rather than to disease progression, and that this resistance may be circumvented by using a non cross-reactive type of IFNα. However, it is still unclear if the same therapeutic strategy can be useful in overcoming acquired resistance to IFNα in the unresponsive patients who are neutralizing-rIFNα Abs negative. For this reason we evaluated the hematological and karyotypic response to lymphoblastoid-IFNα (IFNα-Ly) in 9 Ph+ CML patients in chronic phase who were unresponsive to rIFNα2a and neutralizing-rIFNα2a Abs negative.

Materials and Methods

Patients

Nine Ph+ CML patients in chronic phase who were hematologically and/or karyotypically unresponsive to rIFNα2a and neutralizing-rIFNα2a Abs negative were shifted from rIFNα2a to IFNα-Ly treatment. Two patients were males, 7 patients were

Correspondence: Dr. Domenico Russo, Clinica Ematologica, Policlinico Universitario, piazza S. Maria della Misericordia, Udine, Italy. Fax: international +39.432.559661. Tel. international +39.432.559662-64. E-mail: domenico.russo@drmm.uniud.it
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Table 1. Hematologic and karyotypic response to IFNα-Ly in 9 neutralizing IFNα2a Abs negative patients who were shifted from treatment with recombinant IFNα2a to treatment with

	Previous IFNα2a treatment		IFNa-Ly treatment (hematologic/karyotypic response)					
Pts.	months from start	Response hematologic/ karyotypic	3mo.	6mo.	9mo.	12mo.	24mo.	36mo.
1 EE	44	NR/0	PR	PR	PR	CR/0	CR/0	CR/0
2 Z.V.	13	NR/0	NR	NR				
3 G.C.	6	NR/0	NR					
4 F.M.	31	NR/0	CR	NR	NR			
5 C.V.	24	NR/0	PR	NR				
6 Z.F.	42	NR/0	NR	NR				
7 T.M.	60	CR/0	NR					
8 C.T.	5	CR/0	CR	PR	PR	NR		
9 V.A.	53	CR/0	CR	CR	CR	CR/0	CR	NR

Hematologic response = complete (CR); partial (PR); no response (NR). Karyotypic response = % of Ph negative methaphases.

females; ages ranged between 21 and 61 (median 49). rIFNα2a (Roferon A, Hoffmann La Roche) was previously given in doses ranging from 6 to 9 MU/daily for a median time of 31 months (range 5-60).

nIFNα Abs bioassay

During rIFNα2a therapy, evaluation of neutralizing-rIFNα2a Abs was performed in sera taken 36-72hrs after the last rIFNα2a injection by using IFNα antiviral neutralization bioassay, according to the method previously described.[10] In the same way, monitoring of neutralizing-IFNα-Ly antibodies was also carried out in the patient who underwent subsequent treatment with IFNα-Ly.

Lymphoblastoid IFNα (IFNα-Ly) treatment

IFNα-Ly aWellferon, Wellcome) was administered in an escalating dose of 3 MU/day for the 1st week, 6 MU/day for the 2nd week and 9 MU/day from the 3rd week on. The same dose was continued until a hematologic response (complete or partial) was achieved and maintained. The karyotypic response was evaluated after 12 months in the patients whose hematological response was partial or complete.

Treatment evaluation criteria

The hematologic response was defined as complete (CR) if WBC was less than $10x10^9$/L, without precursors in the differential, the platelet count was less than $500x10^9$/L and the spleen was not palpable. If one of the above criteria did not apply, the response was defined as partial (PR). If two of the above criteria did not apply, the case was classified as non-responsive (NR). The karyotypic response was based on the percentage of Ph neg metaphases and was defined as complete (Ph neg metaphases 100%), partial (Ph neg metaphases 34-99%), and minimal or none (Ph neg metaphases 0-33%).The response was determined by examining more than 20 metaphases. The toxicity was recordered and assessed by using the WHO grading criteria.

Results

Nine neutralizing-rIFNα2a Abs negative CML patients who were hematologically and/or karyotypically unresponsive to rIFNα2a were shifted to IFNα-Ly. The hematologic and karyotypic responses in these 9 patients are shown in Table 1. After the first 3 months of IFNα-Ly therapy, the hematologic response (complete or partial) was reinduced in 3 out of the 6 pts who were non-responsive to previous rIFNα2a therapy, and was maintained in 2 out of the other 3 patients who were hematologically but not karyotypically responsive to rIFNα2a. After 6 and 12 months, the hematologic response was progressively lost, being present only in 3 out of 7 and in 2 out of 3 evaluable patients respectively. None of the hematologically responsive patients achieved a karyotypic response (Ph neg. metaphases = 0%). All of the patients were treated with IFNα-Ly at a dose of 9 MU/day from the 3rd week on, and none of them discontinued IFNα-Ly because of toxicity. One patient (case #1), who was hematologically responsive, continued being treated with IFNα-Ly (9 MU/day) for 36 months but did not achieve any karyotypic response (Table 1). During IFNα-Ly therapy, no induction of neutralizing antibodies directed against IFNα-Ly was observed.

Discussion

The results of this study suggest that, for neutralizing-rIFNα2a Abs negative CML patients who are resistant to rIFNα2a, not only continuation of treatment with rIFNα2a, but also a change in therapy by using a non cross-reactive type of IFNα, such as lymphoblastoid one, would not be advantageous in an attempt to recover a hematologic response. By using IFNα-Ly therapy a durable hematologic response was achieved and/or maintained in only 2 out of 9 patients who were previously hematologically and/or karyotypically unresponsive to rIFNα2a, and none of them obtained a karyotypic response. These results appear to be worse than those previously reported in the CML patients resistant to rIFNα2a and who were neutralizing-rIFNα2a Abs positive.[10] In these patients, shifting from recombinant to lymphoblastoid IFNα produced a long-lasting hematologic response in 6/9 cases.[10] Based on these observations it appears that, for the resistant and neutralizing-IFNα2a Abs negative patients, other therapeutic strategies would be taken into account in an attempt to recover a response. However, as the mechanisms which regulate the sensitivity and resistance to IFNα are still unknown, it is very difficult to adopt direct therapeutic interventions. The addition of other drugs potentially active against Ph+ cells could be considered. In conclusion, since neutralizing-rIFNα Abs may occur in a substantial proportion of CML patients and may be associated with a loss of IFNα

efficacy,[9,10] their monitoring should be taken into account in all of the Ph+ CML patients receiving chronic treatment with recombinant IFNα. A change in therapy by using a non cross-reactive type of IFNα is likely to induce a better hematological response only in the resistant patients who develop neutralizing-rIFNα Abs.

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