short report
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INTERFERON-α2a THERAPY in CML: DISAPPEARANCE OF BCR/ABL TRANSCRIPT IN A CASE OF LONG LASTING CONTINUOUS CYTOGENETIC CONVERSION

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ABSTRACT

Seventy months after the diagnosis, minimal residual disease is undetectable in a patient with Philadelphia chromosome-positive chronic myelogenous leukemia (CML), in long-lasting continuous cytogenetic conversion (CCC) achieved by α2a-interferon (IFN-α) therapy. Fluctuating molecular remission, evaluated with the two stage reverse transcriptase-polymerase chain reaction (RT-PCR) with nested primers , has persisted for two years with the maximum tolerable dose of IFNα (1.5×10^6 UI per day).

Key words: CML, interferon therapy

α-interferon (IFN-α) treatment can produce the reduction of t(9,22) positive clone and the expansion of normal hematopoiesis and it is, up to now, the only pharmacological therapy able to modify the natural history of chronic myelogenous leukemia (CML).[1-3]

The improvement of survival is only expected in subjects treated from early stages of the disease with high doses of IFN-α who obtain a major karyotipic response (i.e. a reduction of more than 65% of Ph^1-positive mytosis). However, complete cytogenetic conversion is achieved in just a minority of treated patients.

Very few cases have been reported where the only therapy with IFN-α yielded a transient eradication of Ph^1 positive hematopoiesis evaluated by polymerase chain reaction (PCR).[4-8]

We herein report the case of a young woman with CML who obtained fluctuating complete molecular remission with IFN-α therapy, during an early and continuous cytogenetic conversion (CCC), that has lasted for more than 5 years.

Case report

A 25-year-old woman was diagnosed to have CML when she was at the 30th week of pregnancy, in September 1988. After the Cesarean delivery carried out a month later, she was recruited in the Roferon A/ABMT protocol of the Italian Cooperative Study Group on CML.[9]

In February 1989, after cytoreductive therapy with hydrossyurea, IFN-α2a treatment, at a dose of 3×10^6 UI/day and than 6×10^6 UI/day, was begun (higher doses of the drug were tolerated only for a short time).

At presentation, DNA analysis revealed the presence of a rearranged band of 5.5 Kb, after digestion with Bgl II restriction endonuclease and hybridization with 32 P-labeled OSI-trans probe (provided by Oncogene Science, Inc, Manhasset, NY), while RNA analysis detected

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the presence of b3a2 transcript.

Hematologic remission was obtained after the first month of treatment and complete cytogenetic conversion was documented at the 12th month.

At the same time molecular analysis was performed and while the specific band in the Southern blot had disappeared in the bone marrow and peripheral blood cell DNA, residual b3a2 transcript could be detected by the nested RT-PCR.

Complete molecular remission was achieved at the 42nd month of treatment and confirmed three months later.[8]

While the research of the rearranged BCR/ABL DNA fragment was always negative in the bone marrow cells from the first molecular test, the b3a2 transcript was detected by PCR six months later and disappeared once more at the 59th month of continuous treatment with IFN-α.

The molecular remission persisted when bone marrow and peripheral cells were examined at the 64th month of treatment.

Discussion

To the best of our knowledge, this is the case with the most lasting CCC that has achieved molecular remission, reported up to now, in which the molecular follow-up has been regularly performed. We have been able to find only eleven other cases of CML, undergoing IFN-α therapy alone, where the two stage PCR failed to detect residual disease.[4-8]

In this patient molecular remission was achieved after 42 months of continuous treatment which was later, in respect to other reports (12th-31st month).

These data show that in this subject, with the maximum tolerable dose of IFN (1.5×10^6 UI per day), the leukemic clone has been gradually reduced.

We do not know how and how long the IFN-α treatment must be prolonged, but the two cases where the therapy was reduced[8] or stopped[6] relapsed after a short time (ten and five months, respectively).

It is expected that the molecular remission could represent an important variable in survival improvement of CML patients,[10] but the reports with molecular studies are rare and the follow-up is still too short to give us conclusive data.

It is therefore important to perform a regular molecular follow-up of the cytogenetic conversions obtained by IFN-α therapy and report complete clinical data in order to identify the best therapeutic approach and the prognosis of long-term good responders.

References

1. Kloke O, Niederle N, Qiu JY, et al. Impact of interferon alpha-induced cytogenetic improvement on survival in chronic myelogenous leukemia. Br J Haematol 1993; 83:399-403.
2. Italian Cooperative Study Group on Chronic Myeloid Leukemia. Interferon alpha-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. N Engl J Med 1994; 330:820-5.
3. Opalka B, Kloke O, Bartram C.R, et al. Elimination by interferon-alpha of malignant clone in chronic myeloid leukaemia. Lancet 1989; 1334.
4. Bartram CR, Yokota S, Hansen-Hagge TE, Janssen JWG. Detection of minimal residual leukemia by polymerase chain reactions. Bone Marrow Transplant 1990; 6(suppl.1):4-6.
5. Martiat P, Maisin, Philippe M, et al. Detection of residual BCR/ABL transcript in chronic myeloid leukaemia patients in complete remission using the polymerase chain reaction and nested primers. Br J Haematol 1990; 75:355-8.
6. Opalka B, Wandl UB, Becher R, et al. Minimal residual disease in patients with chronic myelogenous leukemia undergoing long-term treatment with recombinant interferon-α-2b alone or in combination with interferon-α. Blood 1991; 9:2188-93.
7. Bilhou-Nabera C, Viard F, Marit G, et al. Complete cytogenetic conversion in chronic myelocytic leukemia patients undergoing interferon-α therapy: follow-up with reverse polymerase chain reaction. Leukemia 1992; 6:595-8.
8. Liberati AM, Donti E, Rosso C, et al. Repeated PCR in CLM during IFN-α therapy. Eur J Haematol 1994; 52:152-4.
9. Italian Cooperative Study Group on Chronic Myeloid Leukemia. A prospective comparison of α-IFN and conventional chemotherapy in Ph^+ chronic myeloid leukemia. Clinical and cytogenetic results at 2 years in 322 patients. Haematologica 1992; 77:204-14.
10. Baccarani M, Russo D, Fanin R, Zuffa E, Tura S. Advances in prognosis of chronic myeloid leukemia. Haematologica 1992; 77:377-80.