Philadelphia positive acute lymphoblastic leukemia 16 years after the apparent cure of acute lymphoblastic leukemia. New leukemia or late relapse?

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A Philadelphia-positive ALL in an adult occurring 21 years after the initial diagnosis is reported here. This case raises the question as to whether or not this event is a relapse or a new leukemia. A possible role of interferon-α previously administered to the patient for a chronic viral hepatitis is discussed too.

Acute lymphoblastic leukemia (ALL) relapses occurring more than five years after achieving complete remission (CR) are unusual and raise the possibility of a new neoplasm.

We report a second leukemia 16 years after the cure of a childhood ALL. This second leukemia was Philadelphia chromosome (Ph1) positive, a poor prognostic factor. In addition, we discuss herein the possible role played by interferon-α (IF-α) in the etiopathogenesis of this new leukemia.

Case Report

A three-year-old child affected by ALL in 1974 received induction treatment, holocranial radiotherapy and intrathecal methotrexate and he achieved CR. Maintenance treatment was given until June 1977. After therapy for testicular relapse treatment was stopped in 1979.

In December 1990 a chronic viral C hepatitis was diagnosed and IF-α was given for three years, but was subsequently discontinued as it was ineffective. In 1995, 21 years after the first diagnosis the patient presented with clinical and analytical signs of an apparent ALL relapse. Immunophenotyping revealed a B lineage common ALL. Reverse-transcription polymerase chain reaction (RT-PCR) with nested primers specific for minor breakpoint rearrangements (primers supplied by Oncogen RP, Cambridge, MA, USA) was positive giving rise to the expected bands in bcr/abl e1a2 rearrangements. No amplification was noted when transcripts from the patient were assayed with primers specific for major breakpoint rearrangements.

After receiving a single chemotherapy course, he died of septic abdominal infection.

In patients achieving long-lasting CR, late relapses are unusual and raise a controversial issue: relapse versus new leukemia.

Pagano et al. revealed that the actuarial estimated cumulative proportion of ALL patients with a secondary haematologic neoplasm at 5 and 10 years were 0.59% and 3.63%, respectively.

In our case, the lack of immunologic and molecular data from the first leukemia hampers understanding of whether we are facing a genuine relapse or a distinct ALL. The hypothesis of a different neoplasm is supported by two facts. Firstly, the strikingly long duration of our patient’s relapse-free survival (therefore, a drug-induced leukemia cannot fully discarded). Secondly, although in pediatric ALL, Ph1 can be absent at diagnosis, subsequently emerging as a consequence of clonal evolution, and a subset of good prognosis Ph1 ALL could exist, Ph1 is usually associated with aggressive disease, poor prognosis and no short term remissions.

Nevertheless, a relapse cannot be completely ruled out. In this case IF-α, as an immune modulator, administered to the patient in previous years may have prompted the leukemia relapse.

IF-α can activate B-cells in malignant and non-malignant lymph nodes to proliferation and blast transformation. IF-α has been shown to regulate B-cell differentiation and to act as a natural regulator of B-cell functions. In some neoplasms of B-cell origin, especially myeloma, IF-α is able to stimulate the proliferation of Interkeukin-6 dependent cells of clonogenic tumor cells in vitro as well as in vivo.

Key words

Acute lymphoblastic leukemia, late relapse, Philadelphia chromosome, interferon-α.

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References

The bcr-abl rearrangement in T-lineage ALL has been rarely described. In the last three years we studied all new patients with ALL at diagnosis by cytogenetic and molecular analysis. Three out of ten T-lineage ALL patients presented the rearrangement and only one was Philadelphia positive.

The Philadelphia (Ph) chromosome, t(9;22) (q34;q11), is present in more than 95% of patients with chronic myelogenous leukemia (CML) and in 15-25% of adults with acute B-lineage lymphoblastic leukemia (ALL).\(^{1,2}\) In T-lineage ALL it has rarely been reported\(^ {3,4}\) and singular cases of T-lineage adult ALL carrying the bcr-abl rearrangement have been recently described.\(^ {5,6}\) bcr-abl rearrangement in T-lineage ALL is thus a rare event and the clinical relevance of this translocation is currently unknown.

In the last three years we studied 25 new consecutive cases of ALL (14 B-lineage and 11 T-lineage). We present here the clinical, immunologic, cytogenetic and molecular features of three out of five T-lineage ALL patients presenting bcr-abl rearrangement at diagnosis.

**Patient #1.** A 15-year-old male was referred with a recent history of cough and fatigue. He was treated with daunomycin, vincristine, asparaginase, and prednisone and obtained a complete remission. He relapsed 7 months later, did not obtain a second remission and died 4 months later.

**Patient #2.** A 32-year-old male was admitted with acute leukemia. He was treated with idarubicin, cytarabine, vincristine and prednisone and obtained complete remission. He was later submitted to allogeneic peripheral blood transplantation from his HLA-identical sister while in first CR. The patient developed acute but not chronic GvHD. He relapsed 18 months later. He is actually in second CR after reinduction treatment.

**Conclusions.** The Philadelphia chromosome is an uncommon translocation in acute lymphoblastic leukemia. Its incidence may be underestimated in clinical practice. The clinical relevance of bcr-abl rearrangement in T-lineage ALL remains to be established.