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Editorial, comments & views

Eosinophilia in leukemias: a probable leukemic clone

Eosinophilia can be associated with several types of malignant medullary hematopoietic disorders such as chronic myelogenous leukemia, some subtypes of acute myeloblastic leukemia (AML), lymphoblastic leukemia (ALL), and myelodysplastic syndromes (MDS). When the eosinophilic lineage is the only leukemic clone, eosinophilic leukemia must be recognized. However, the distinction between truly malignant eosinophilic leukemia and an idiopathic hypereosinophilic syndrome is difficult because it depends on proving whether eosinophilia is produced by a clonal or a reactive disorder.[1,2] Clonality must be demonstrated with methods such as cytogenetics, fluorescence *in situ* hybridization (FISH) and/or polymerase chain reaction (PCR). Results from these analyses can also be helpful to prove whether eosinophils are malignant or reactive, when eosinophilia is associated with leukemia. In some cases, eosinophilia has been shown to be part of the malignant clone, especially in some subtypes of AML, such as the AML M4eo and in myelomonocytic leukemia. Abnormalities of chromosome 16 involving the q22 region are associated with such a disease. In other cases, the leukemic cells themselves produce cytokines that stimulate the production of eosinophilic cells. Interleukin-5 (IL-5) is known to stimulate eosinophilopoiesis.

A wide range of abnormal karyotypes has been described in patients with malignant hematopoietic disorders with eosinophilia, including rearrangement of the long arm of chromosome 5, trisomy 8 and rearrangement of the short arm of chromosome 12. The gene encoding IL-5 forms a cluster on chromosome 5, and the occurrence of deletions and translocations of chromosome 5 with breakpoints at or near this site suggest that these oncogenes may be involved in such hematologic malignancies.

The gene involved in forming a cluster in the region of the short arm of the chromosome 12 should be ETV6, a transcriptor factor in the Ets family. The apparently non-random association of this region of chromosome 12 (12p13) and eosinophilia in leukemia is strengthened by further cases in literature. t(5 ;12)(q33 ;p13) was described in some cases in which eosinophilia was associated with leukemia. This particular chromosomal translocation suggests that eosinophils participate in the leukemic clone. The rearrangement of 12p13 with other different breakpoints has also been reported. It was recently shown that a fusion transcript between the Ets family gene (ETV6) and the tyrosine kinase domain gene (ABL1), located on 9q34 or not, results from a different translocation. This rearrangement was linked to acute or chronic hematologic malignancy. In such cases, morphologic abnormalities of eosinophils were observed.[3]

La Starza *et al.*[4] describe and analyze two cases of hematologic malignancies associated with eosinophilia. They show that the eosinophils were morphologically abnormal cells and that they were clonal. In each case, there was a rearrangement of the short arm of chromosome 12 (12p13), where the ETV6 gene is located, associated with the short arm of chromosome 8 (8p21) in the first case and with the long arm of chromosome 9 (9q34), where the ABL1 gene is located, in the second case. FISH and/or PCR were performed and the results showed an ETV6/ABL1 fusion in both cases. Since the ETV6/ABL1 protein displays tyrosine kinase activity, it could be suggested that eosinophilia in such leukemias directly results from gene fusion. The tyrosine kinase activity resulting from this fusion could have important implications for therapy using new drugs such as a new inhibitor of the breakpoint cluster region of ABL tyrosine kinase. Although ETV6/ABL1 is rare in medullary hematopoietic disorders, the paper by La Starza *et al.* suggests that it would be useful to look for the fusion when eosinophilia seems to be part of the leukemic clone.

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Strategies other than dose-intensification should be pursued in elderly patients with untreated acute myeloblastic leukemia

Commenting the paper by Schaich *et al.*,[1] Dr. Estey properly concludes that strategies other than dose-intensification should be pursued in elderly patients with untreated acute myeloblastic leukemia (AML). Despite several trials, the prognosis of AML in the elderly remains poor, as confirmed also by two recent studies in this journal.

Ferrara *et al.*[2] studied 150 consecutive patients to investigate whether aggressive salvage chemotherapy results in an actual survival advantage in elderly patients with relapsed AML, and to compare hospitalization and load of supportive treatment between patients receiving aggressive management or only palliation. They concluded that aggressive chemotherapy results in an actual survival advantage only for a minority of elderly patients with relapsed AML, i.e. those with first complete remisxsion lasting for more than 12 months.

Veneri *et al.*[3] reported on 69 consecutive AML patients aged ≥ 66 years. Their study did not provide any evidence in favor of intensive treatment for non-M3 AML in the elderly. The authors raised the question of whether an aggressive treatment, although of some benefit for a minority of cases, should ever be applied to this setting of patients.

Using induction regimens designed to reduce toxicity and new drugs may represent an alternative strategy,[4] although these results require confirmation a larger prospective trials.

We need to learn much more about the biology of AML in the elderly[5-8] and to define novel criteria for risk stratification,[9,10] before useful therapeutic strategies can be developed.

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Inside Haematologica: new concepts in the management of multiple myeloma

In the last few years, the management of multiple myeloma has changed considerably with the identification of new biological markers, the adoption of novel transplantation approaches and the use of thalidomide.[1-12] In this issue, three studies mark these changes.

Cytogenetic studies have previously shown that 13q- and monosomy 13 can be found in several patients with multiple myeloma, and that these abnormalities might be associated with an adverse outcome.[7] Nomdedeu *et al.*[13] have performed a genotyping analysis on purified neoplastic plasma