

ferent ( $p < 0.05$ ) from the overall mean frequency of allele  $\alpha^{\text{LELY}}$ , and whether frequencies were significantly different ( $p < 0.05$ ) within any particular pair of groups, the  $m \pm 2s$  interval being used in all cases.

We found that the distribution of  $\alpha/\alpha$ ,  $\alpha/\alpha^{\text{LELY}}$  and  $\alpha^{\text{LELY}}/\alpha^{\text{LELY}}$  individuals was: 91(52%), 71(41%) and 13(7%), respectively (Figure 1a). Out of 350 *SPTA1* genes (Figure 1b), we found 97  $\alpha^{\text{LELY}}$  alleles, which corresponds to a frequency of 0.28. Exon 40 and exon 45 mutations were always found to be linked. The frequency of allele  $\alpha^{\text{LELY}}$  in Greek Caucasians was thus almost identical to that recorded among French Caucasians. The overall mean of all available frequencies,<sup>5,6</sup> including this work, ( $n=866$  *SPTA1* allele), was  $m=0.22 \pm 0.087$ . The only statistically significant difference ( $0.01 < p < 0.05$ ) was that for the pair of Caucasians and Parakana Indian groups (Table 1).

The Greek and French populations are both of Caucasian origin<sup>7</sup> and thus could be expected to have similar frequencies of the  $\alpha^{\text{LELY}}$  and this expectation is supported by all experimental evidence (ref. #5 and present study). Allele  $\alpha^{\text{LELY}}$  also appears with similar frequencies in remote ethnic groups<sup>5,6</sup> yet not as uniform as within Caucasians.

The significant difference between the Caucasian population and Parakana Indians ( $0.01 < p < 0.05$ ), noted here, shows that the  $\alpha^{\text{LELY}}$  polymorphism, although relatively constant throughout the world, is less so in very isolated populations. Parakana Indians form a very ancient population and have a very restricted range of polymorphisms for several genetic markers.<sup>8</sup>

$\alpha^{\text{LELY}}$  is deleterious only in *trans* of *SPTA1* alleles that cause HE and may reach a non-negligible proportion in black populations;<sup>9</sup> this issue has not yet been evaluated in Greek populations.

The presumably universal character of  $\alpha^{\text{LELY}}$  is consistent with a very ancient origin. The present study underscores the high stability of allele  $\alpha^{\text{LELY}}$  among Caucasians and even non-Caucasians with exception of the Parakana Indians.

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### Key Words

*SPTA1* gene, low expression allele  $\alpha^{\text{LELY}}$ , Greek population

### Funding

This work was supported by grants from the General Secretariat of Research and Technology of the Greek Ministry of Industry, Energy and Development (Program PFOR to LHM) and Athens University (to LHM and ISP), Greece.

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### Acute myeloid leukemia occurring in a patient with polycythemia vera in treatment with hydroxyurea

Sir,

Hydroxyurea is a non-alkylating chemotherapeutic agent used in the treatment of patients with polycythemia vera (PV). The leukemogenic risk associated with treatment with hydroxyurea alone is considered to be relatively low but the probability of development of acute leukemia has been recognized as a long-term side-effect.<sup>1</sup> We report the case of a patient with PV who developed acute myeloblastic leukemia (AML) after three years of treatment with hydroxyurea.

A 62-year old man was admitted because of leukocytosis and thrombocytosis in February 1995. Clinical examination revealed only splenomegaly of 3 cm. Full blood count was erythrocytes  $5.630 \times 10^9/\text{L}$ ; hemo-

**Table 1. Criteria for diagnosis of PV.**

PVSG criteria	Patient's data
1. Elevated red blood cell mass	N.A.
2. Normal ABG	Yes
3. Splenomegaly	Yes
4. Thrombocytosis and leukocytosis	Yes
5. Bone marrow trilinear hyperplasia	Yes
6. Low serum EPO levels	N.A.
7. Abnormal marrow proliferative capacity to form erythroid colonies in the absence of exogenous EPO	N.A.

**Table 2. Criteria for diagnosis of AML**

Cytochemistry	MPO	+++
Immunophenotype	HLA-DR	55.4%
	CD34	89%
	CD117	84.6%
	CD33	0.2%
PCR analysis	BCR/ABL	negative

globin: 15.7 g/dL; hematocrit: 51%; platelets:  $1,536 \times 10^9/L$ ; leukocytes:  $32 \times 10^9/L$ . Bone marrow biopsy showed erythroid, granulocytic, and megakaryocytic hyperplasia. Arterial blood gas analysis showed a  $SpO_2$  of 92%. According to PVSG criteria the diagnosis of classic PV was made (Table 1). The patient was treated with hydroxyurea at the dose of 25 mg/kg/day PO for 30 days, followed by low-dose maintenance of 15 mg/kg/day for 20 days a month. Complete remission was achieved after 11 months of such treatment. Low-dose hydroxyurea was maintained after remission. In February 1998 the patient returned to our hospital because of thrombocytopenia and a leukocyte count of  $6.6 \times 10^9/L$  with 60% blast cells. Bone marrow aspirate revealed replacement of normal elements by 40% myeloblasts of FAB M1 morphology that were myeloperoxidase positive (+---). Immunophenotyping studies showed that the blasts were positive for CD34, HLA-DR, CD117, and negative for CD33. The diagnosis of AML FAB M1 was made (Table 2). PCR analysis did not reveal the presence of BCR/ABL. The patient was treated with idarubicin but died six months later.

In this report we describe a patient with AML occurring after an initial diagnosis of PV treated with hydroxyurea alone. The evolution to acute leukemia is a natural event of this malignant disorder, but rarely occurs during the initial eight years of disease.<sup>2</sup> Its development can, however, be induced by therapeutic intervention. The leukemogenic risk of radioactive phosphorus or alkylating agents in the treatment of PV has led to the increased use of hydroxyurea.<sup>3</sup>

Hydroxyurea is a antimetabolite that interferes with DNA synthesis by inhibiting ribonucleotide reductase.<sup>4</sup> Although not directly genotoxic, hydroxyurea might impair the repair of damaged DNA, raising a concern regarding mutagenicity. Najean *et al.* observed that the risk of leukemic transformation after treatment with hydroxyurea was approximately 10% at the 13<sup>th</sup> year.<sup>5</sup>

Our patient developed AML after three years of treatment with hydroxyurea at the same doses used by Najean *et al.* Our finding suggests that this first-line therapy for PV patients remains debatable. In young patients hydroxyurea should be avoided and therapy should be limited to phlebotomy alone or to the use of interferon- $\alpha$ .<sup>6</sup> Only patients who do not achieve complete remission with interferon- $\alpha$  might receive hydroxyurea in an intermittent schedule. In elderly patients the use of hydroxyurea remains the treatment of choice.<sup>7</sup> In conclusion, hydroxyurea is not a safe drug. Too little is yet known about the mutagenic potential of this drug and therefore caution over its use and a close follow-up of patients treated with hydroxyurea is required.

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### Key words

Polycythemia vera, AML, hydroxyurea.

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