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Key words: HUMARA, essential thrombocythemia, polycythemia vera, clonality.

Acknowledgments: the authors wish to express their gratitude to Dr. M. Albitar (University of Texas MD Anderson Cancer Center, Houston) for his valuable advice on the development of the HUMARA assay and to Mercè Musset, Rosa M. Vila, Carme Melero and Rosa Navarro for their valuable technical contribution to the study. Finally, Joan Vila (IMIM) helped in the statistical analysis.

Funding: this work was supported by grants PI030345 from the "Ministerio de Sanidad y Consumo", SAF-2001-4947 from the "Ministerio de Ciencia y Tecnología", and Red de Centros de Cáncer C03/07 from the "Instituto de Salud Carlos III", Spain.

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Chronic Myeloproliferative Disorders

Safety profile of hydroxyurea in the treatment of patients with Philadelphia-negative chronic myeloproliferative disorders

The efficacy of hydroxyurea (HU) in myeloproliferative disorders is well documented. HU controls thrombocytosis both in polycythemia vera (PV) and in essential thrombocythemia (ET), while reducing the risk of thrombosis.[1] Despite many anectodal reports, no evaluation of the prevalence and type of side effects of HU exists in large series of patients.

haematologica 2005; 90:261-262
(http://www.haematologica.org/journal/2005/2/261.html)

This is a retrospective study of 75 patients with ET and 54 with PV (53 males, 76 females, mean age 58,12±14,68 years) diagnosed in agreement with the Polycythemia Vera Study Group criteria[2,3] and treated with HU (median follow-up 7.18 years) at our Department over the last 20 years. HU (Oncocarbide®, 500 mg) was given to reduce platelet count (induction dosage 30 mg/kg/day and maintenance 15 mg/kg/day), for one or more of the following reasons: (i) age over 60 years; (ii) previous major thrombotic event; and (iii) platelet count over $1,500\times10^9$/L.[1] The achievement of a platelet count $<600\times10^9$/L was considered a complete response (CR), while, if the platelet count remained $>600\times10^9$/L within 6 months of HU therapy, the drug treatment was considered to have failed. All side effects and toxic effects of HU were recorded; if a side effect did not require drug withdrawal it was considered a minor effect.

One hundred and twenty patients (93%) achieved a CR in a median time of 1 month (range 1-13 months). In 9 cases the drug treatment failed (7%). In 106 patients (88% of CR) HU was successfully continued without relevant complications over a median follow-up of 6.74 years to date (median 3.67 years). No hemorrhages but 15 thrombotic complications (4 cerebrovascular, 5 coronary, 1 peripheral arteries and 5 deep vein thrombosis in 2 cases with pulmonary embolism) were documented during HU therapy.

Minor effects. An increase of MCV (>98 fL) over normal levels occurred in 54 patients (45% of responders) within the first 6 months of therapy; this is a well known and usually negligible side effect of HU. However, 19 females and 13 males developed severe macrocytosis (MCV > 110 fL) within one year of treatment. One of these patients had black nail pigmentation which disappeared within three months after drug discontinuation; two more patients had black nail pigmentation, which was stable over time. This is an uncommon finding of not paramount importance.

Major effects. In 2 patients the drug was withdrawn because of symptomatic anemia (Hb less than 85 g/L) with MCV >130 fL occurred.[4] In both cases, more than 20 mg/kg/day HU was given. Twelve patients came off the drug because of toxic effects certainly or probably due to HU (2 fevers, 2 allergies, 4 leg ulcers, 3 acute leukemias, 1 cancer) (Table 1). This rate of necessary HU discontinuation was 1.6×100 patients/year.

Fever occurred after 2 and 3.5 days of therapy in 2 patients. In both cases, we made another treatment attempt which again resulted in fever. Fever can be

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Table 1. Side effects of hydroxyurea (HU) in our patients with polycythemia vera (PV) and essential thrombocythemia (ET).

	N° of cases	Sex F/M	PV/ET	HU mean dose (mg/day)	Median treatment duration (days)
Total patients	129	76/53	54/75	620±270	1,299
Drug failure	9	5/4	3/6	1550±560	180
Complete response	120	71/49	51/69	600±245	1,310
Thrombotic complication	15	6/9	9/62	890±260	890
Early major side effects	4	1/3	1/3	1000±500	5
Late major side effects	10	7/3	3/7	750±250	1,200
Minor side effects (black nail pigmentation and macrocytosis without anemia)	54	36/18	19/37	620±270	1,310

caused by virtually any drug, due to immunological and/or a local inflammatory reaction.[5] Two patients had cutaneous erythema, associated in 1 case with transient pancytopenia and in the other with transient liver failure that rapidly resolved (10 days) after drug withdrawal. No other drug was involved in either case. Four females older than 60 years old (2 over 80) on HU (total dose 0.9-2.4 kg) for at least 3 years suffered from painful leg ulcers. None of them had diabetes. Three of them recovered within 1 month after drug withdrawal and were already being followed at our clinics. The other patient, who had undergone left leg Fogarty's embolectomy 3 years previously, was referred to us after having continued treatment elsewhere for 3 months following appearance of the ulcer. Two further weeks later she underwent leg amputation because of intractable local infection and pain and finally died of myocardial infarction. Painful malleolar ulcers appear despite the lack of trauma or provoking agents other than HU. Most cases, as ours, had received about 1g/day of HU per day for at least 1 year. These ulcers seem to result from cumulative toxicity of HU on the basal layer of the epidermidis due to inhibition of DNA synthesis. Treatment is difficult but must include prompt cessation of HU therapy.[6]

It has been suggested that HU treatment in myeloproliferative disorders increases the risk of acute leukemia. Besides some series reporting a nearly 10% risk by the 13th year of treatment, others stressed that leukemic transformation occurs in patients treated with other cytotoxic drugs.[7] Our 3 patients who developed acute leukemia had received busulfan (BU) in the first period of their disease for 9 and 15 months, followed by a median of 7.5 years of HU treatment.[8] The patient who developed pancreatic cancer had received BU and HU.[9] However, a relation between HU and such a cancer seems improbable. We conclude that HU is a safe and useful drug in the treatment of myeloproliferative disorders. Prompt recognition of side effects, which are mostly minor and rapidly subside once the drug is withdrawn, is crucial in order to avoid more severe complications.

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Acute Myeloid Leukemia

Trisomy 11 in myeloid malignancies is associated with internal tandem duplication of both *MLL* and *FLT3* genes

In 20 patients with myeloid malignancies and isolated trisomy 11 an internal tandem duplication of the *MLL* and *FLT3* genes was observed in 41% and 31% of the cases, respectively; 80% of the *FLT3*+ cases showed *MLL* self-fusion. Concomitant presence of *MLL* and *FLT3* anomalies could be relevant in determining the poor outcome of patients with acute myeloid leukemia with trisomy 11.

haematologica 2005; 90:262-264
(*http://www.haematologica.org/journal/2005/2/262.html*)

Isolated trisomy 11 is a rare aberration observed in myelodysplastic syndromes (MDS) and acute myeloblastic leukemia (AML). Molecular characterization of cases of AML with trisomy 11 has revealed a non-random association with a partial tandem duplication (PTD) of the *MLL* gene, leading to in-frame fusion of a portion of the proto-oncogene with itself.[1] The incidence of this molecular anomaly in trisomy 11 cases of AML ranged from 20% to 73%.[1-3] Internal tandem duplication (ITD) has been demonstrated as a oncogene-activating mechanism also in another gene involved in AML, namely the *FLT3* gene, which encodes for a receptor tyrosine kinase widely expressed in hemopoietic cells and precursors.[4]

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