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.

Maria Luigia Randi, Elisabetta Ruzzon, Guido Luzzatto, Fabiana Tezza, Antonio Girolami, Fabrizio Fabris

Internal Medicine, Department of Medical and Surgical Sciences, University of Padua Medical School, Padua, Italy

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Correspondence: Maria Luigia Randi, MD, Dept. of Medical and Surgical Sciences, via Ospedale 105, 35128 Padua, Italy. Phone: international +39.049.8212668. Fax: international +39.049.8211391. E-mail: marialuigia.randi@unipd.it

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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.

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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]

Table 1. Clinical data of the patients with trisomy 11.

Case	Sex/Age	Diagnosis	Clinical data and treatment	Karyotype	MLL/PTD	FLT3/ITD	Cause of death	Survival (months)
1	81	RAEB	Supportive	+11 / +8,+11	ND	ND	Sepsis	2
2	66	RAEB	Decitabine, refractory	+11	–	ND	Infection	22
3	77	RAEB	Decitabine, refractory	+11	–	–	Progression	19
4	76	RAEB	Supportive	+11 / +8,+11	–	–	Progression	4
5	74	MPD, accelerated	HU, transfusions	+11	–	–	Progression	18
6	36	AML-M0	Ara-C+Dauno, alloBMT in CR1	+11	ND	ND	/	124+
7	67	AML-M1	ARA-C+Dauno, CR1 1 month	+11	+	+	Infection	2
8	52	AML-M1	Ara-C+ Dauno+VP16, auto-SCT CR1 9 months	+11	+	+	Relapse	15
9	66	AML-M1	Ara-C+Mito+VP16	+11	–	+	Toxicity	2
10	47	AML-M2	ARA-C+Ida, CR1 37 months	+11	ND	ND	Colon adenocarcinoma	37
11	53	AML-M2	Ara-C+Dauno, CR1 18 mo, CR2 10 mo	+11 / +11,+13	–	–	Relapse	37
12	63	AML-M2	NA	+11	–	–	NA	Lost
13	61	AML-M2	Ara-C+Dauno, refractory	+11	–	–	Progression	14
14	73	AML-M6	Ara-C+Ida, CR1 14 months	+11	+	–	Relapse	28
15	73	AML	NA	+11	+	+	NA	Lost
16	79	AML post-MDS	Ara-C+Adria, CR1 15 months	+11	–	–	Relapse	18
17	52	t-AML-M1	Low-dose Ara-C	+11	+	–	Progression	6
18	62	AML post-MDS	Mito+Ara-C +VP16, CR1 22 months Relapse, FLANG, CR2	+11	–	–	/	54+
19	59	AML post-MDS	FLAG	+11	+	+	Toxicity	2
20	92	AML post-CMML	HU for CMML, VP16 for AML	+11,+13	+	–	Progression	12

NA: not available; ND: not done; CR1: first complete remission; CR2: second complete remission; SCT: stem cell transplant; BMT: bone marrow transplant; HU: hydroxyurea; Flu: fludarabine; Dauno: daunoblastine; Mito: mitoxantrone; Ara-C: cytosine-arabinoside; VP16: etoposide; FLANG: flu+mito+Ara-C+G-CSF; FLAG: flu+Ara-C+G-CSF.

FLT3/ITD occurs in approximately 20% of unselected adult patients with *de novo* AML and in 30-40% of AML with a normal karyotype.[5] Co-duplication of *MLL* and *FLT3* was observed[3] in two cases of AML. It has been reported that *FLT3*/ITD is more common in patients with *MLL*/PTD (33%) than in cases with *MLL* translocations (8%). In a large series of adult AML analyzed for both molecular anomalies, the rate of *MLL*/PTD was significantly higher in *FLT3* positive (8.7%) than in *FLT3* negative (4.1%) patients, although this finding did not correlate with trisomy 11.[6]

In 20 patients with myeloid malignancies carrying a trisomy 11 as a primary anomaly we analyzed clinical, immunological and cytogenetic data and correlated them with the presence of the *MLL*/PTD and *FLT3*/ITD (Table 1). Bone marrow cells at diagnosis were studied for +11 by fluorescent *in situ* hybridization (FISH) with a centromeric probe for chromosome 11. The *MLL* gene was investigated with a combination of two PAC clones that cover the *MLL* gene with a minimal overlap in the breakpoint cluster region.[7] Control experiments were performed on 10 normal bone marrow samples. The normal range was set as the mean +3SD. Southern blotting for the *MLL* gene[2] and reverse transcription polymerase chain reaction (RT-PCR) identification of *MLL* and *FLT3*/ITD were done as reported elsewhere.[1,8]

The diagnosis was AML, either *de novo* or secondary, in 15 patients, MDS in 4 cases, and accelerated myeloproliferative disorder in one case. Immunophenotyping showed consistent positivity for stem/progenitor cell markers, including CD34, HLA-DR, CD33 and CD13. Interphase FISH analysis confirmed the trisomy in all cases, in a percentage of cells ranging from 17% to 82%. *MLL*/PTD was observed in 7/17 (41.2%) cases, 6 with isolated trisomy 11 and one with additional anomalies. *FLT3*/ITD was analyzed in 16 patients and was found to be positive in 5 cases (31.2%). No case of MDS showed a structurally altered *MLL* or *FLT3* gene, so the incidence of the two anomalies in AML patients was 54% and 38%, respectively. The overall incidence of *FLT3*/ITD was similar to that observed in patients with normal karyotype. However, 4 out of 5 (80%) of the *FLT3*/ITD positive cases also showed *MLL*/PTD, whereas only 3/11 (27.3%) of the *FLT3*/ITD-negative cases had *MLL*/PTD. Considering the *MLL*/PTD-positive cases, *FLT3*/ITD was found in 4/7 (57.1%), whereas only 1 of the 10 *MLL*/PTD-negative patients had *FLT3*/ITD. The median survival for the whole group of +11 cases was 14.5 months, 18 months for both the *MLL* and *FLT3* negative groups and only 6 and 2 months for the patients who had a *MLL* or a *FLT3* duplication, respectively (Figure 1). Recently, co-duplication of *MLL* and *FLT3* genes has been suggested as a possible marker of a common genotoxic stress;[5] alternatively, it has been suggested that *MLL* rearrangements and *FLT3* constitutive activation may cooperate in transformation.[9] In our group of patients with trisomy 11, a close correlation was found between the two anomalies with a high percentage of co-duplication when compared to patients showing isolated duplication of *MLL* or *FLT3*.

The pathogenetic mechanism by which the *MLL* partial duplication leads to carcinogenesis is not clear. Recently, amplification of the *MLL* gene has been identified as a new consistent cytogenetic mechanism of *MLL* activation,[7] mediated by the upregulation of a number of other genes.[10] The gene expression profile in patients with *MLL* amplification is similar to that observed in *MLL*-rearranged acute leukemia.[10] In patients with trisomy 11, the presence of a low-copy *MLL* amplification may have an etiologic role based on *MLL* gain of function.

FLT3/ITD appears to be quite common in patients with *MLL* self-fusion; it remains to be clarified whether the co-expression of the two anomalies may depend on a common pathogenetic mechanism or merely represent co-operation in multistep leukemogenesis, possibly being

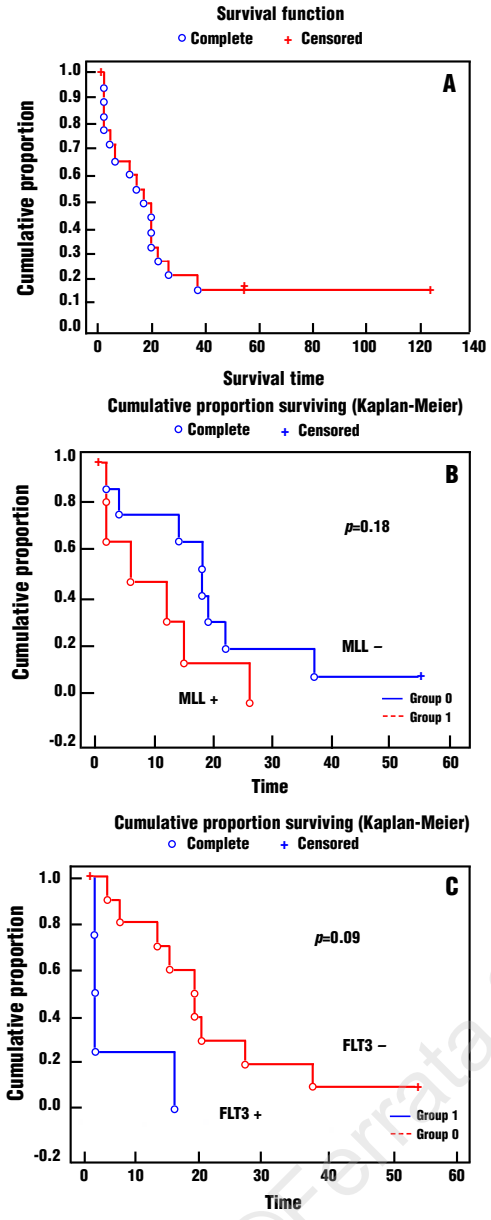

Figure 1. A. Kaplan-Meier survival curves of all patients with trisomy 11 (n=20). B. Group 0: patients negative for *MLL*-PTD (n=10); group 1: patients positive for *MLL*-PTD (n=7). C) group 0: patients negative for FLT3-ITD (n=11); group 1: patients positive for FLT3-ITD (n=5).

relevant in determining the poor outcome observed in patients with trisomy 11.

Giovanna Rege-Cambrin, Emilia Giugliano,*° Lucienne Michaux,° Michel Stul,° Patrizia Scaravaglio,* Anna Serra,* Giuseppe Saglio,* Anne Hagemeijer°*

**Department of Clinical and Biological Sciences, Osp. S. Luigi Gonzaga, Orbassano, Italy; °Center for Human Genetics, University of Leuven, Belgium*

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Correspondence: Dr. Giovanna Rege-Cambrin, Medicina Interna II, Dipartimento di Scienze Cliniche e Biologiche, Ospedale S. Luigi Gonzaga, 10043 Orbassano (TO), Italy. Phone: international +39.011.9026608 Fax: international +39.011.9038636. E-mail: giovanna.rege@inwind.it

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Acute Lymphoblastic Leukemia

γδ and αβ T-cell acute lymphoblastic leukemia: comparision of their clinical and immunophenotypic features

γδ-T-cell acute lymphoblastic leukemia (ALL) is a rare variant of ALL. The comparison of some clinical and laboratory features in children and adults with γδ-T-ALL or αβ-ALL showed that in γδ-T-ALL the CD45RA⁻/CD45RO⁺ phenotype was predominant, the hemoglobin concentration was lower in children and the presence of splenomegaly and the white cell counts was higher in adults.