

# Anagrelide for Treatment of Patients with Chronic Myelogenous Leukemia and a High Platelet Count

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**ABSTRACT:** Chronic myelogenous leukemia (CML) is usually treated with hydroxyurea or interferon- $\alpha$ . In some patients high platelet counts develop although leukocyte counts are well controlled with these drugs. If in such a situation cytoreductive therapy has to be intensified by a increase of the dosage, anemia and leukocytopenia as well as adverse effects of the drugs are likely to occur. In twelve CML patients we have therefore combined the basic CML treatment with anagrelide. This drug which selectively reduces platelet counts has been shown to be efficacious in the control of thrombocytosis in essential thrombocythemia. The diagnosis had been confirmed in all CML patients by cytogenetic and/or molecular biological analysis. The median age of our group was 58 years. Five were women and seven men. All patients were on treatment with hydroxyurea, some of them had previously received treatment with interferon- $\alpha$  (alone or in combination with hydroxyurea), busulfan or melphalan. Prior to the initiation of anagrelide treatment the platelet count was between 970,000 and 3,600,000/ $\mu$ l (median about 2,000,000/ $\mu$ l). Seven patients had thrombohemorrhagic complications. All twelve patients, experienced hematologic responses, since their platelet counts decreased to less than 600,000/ $\mu$ l. The median platelet count after reduction was 343,000/ $\mu$ l. The median dosage required to achieve these responses and to maintain them for a period of at least four weeks was 1.9 mg/day. Thrombohemorrhagic complications disappeared or did not recur in all symptomatic patients. Adverse effects were seen in 3/12 patients: headache (1), tachycardia (1), palpitation (1) and fluid retention (1). Whereas these symptoms were mild and transitory they caused one patient to request discontinuation of treatment. Currently five patients are still on treatment with anagrelide (median duration of treatment 11 months) while therapy had to be discontinued in the seven others because of bone marrow transplantation, development of osteomyelofibrosis, blast crisis or on patient request. In our experience anagrelide is a useful therapeutic adjunct when thrombocytosis in patients with CML cannot properly controlled alone with traditional drugs.

**Keywords:** chronic myelogenous leukemia, thrombocytosis, anagrelide, hydroxyurea

## INTRODUCTION

Chronic myelogenous leukemia (CML) is a clonal disorder of the hematopoietic system. It is characterized by an excessive expansion of myelopoiesis and often megakaryocytopoiesis. During chronic phase patients are treated with

interferon- $\alpha$  or hydroxyurea (1). In most patients elevated peripheral blood cell counts and splenomegaly can be properly controlled with these drugs. Some individuals, however, develop high platelet counts during therapy which could only be controlled by an increase of the dose of interferon- $\alpha$  or hydroxyurea which leads to

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myelosuppression and/or unacceptable adverse effects. In such a situation an agent selective for the reduction of platelet counts would be an ideal adjunct to the treatment. We have therefore evaluated the efficiency of anagrelide for such patients. Anagrelide is a new platelet lowering agent (2) which has been shown to be efficacious and safe in patients with essential thrombocythemia (3,4).

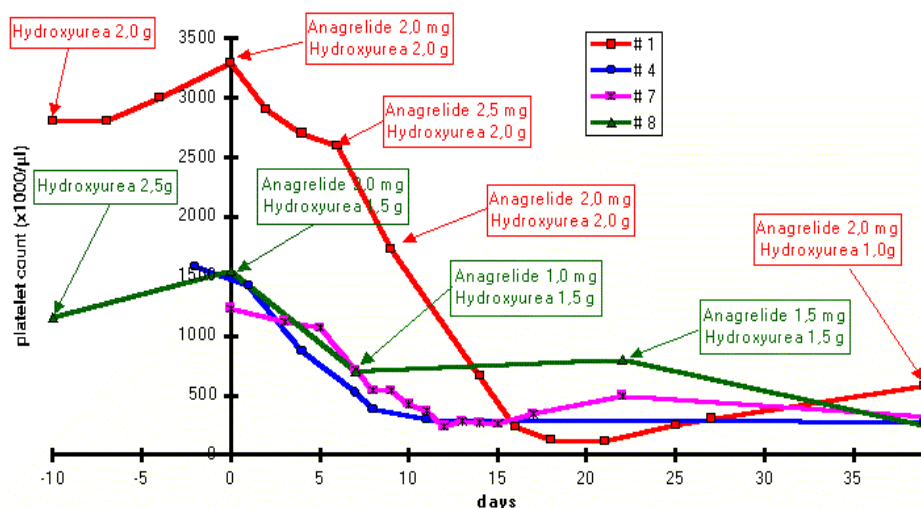
## PATIENTS AND METHODS

We have entered twelve patients with CML into our study. Hematological diagnosis had been confirmed by cytogenetic and/or molecular biological analysis. The patients were treated

according to a protocol which had been approved by the Research Ethics Committee of the University of Munich Medical School. Patients were informed and gave written consent. Inclusion criteria were age above 18 years and diagnosis of CML with platelet counts above 900,000/ $\mu$ l which could not be controlled with other drugs. Treatment was initiated with an oral daily dosage of 2.0 mg and the dosage increased by 0.5mg/day after one week when there was no appropriate decline of the platelet count. The drug was provided by Roberts Pharmaceuticals, Eatontown, NJ, USA. Patients were seen in regular time intervals when physical examinations, blood cell counts and routine blood chemistry analyses were performed.

**Table 1.** Patients with CML and a high platelet count (abbreviations: Age = age at the initiation of anagrelide therapy; S = Symptoms prior to anagrelide treatment: M = Microcirculatory disturbances, T = Thrombosis, B = Bleeding), ASA = Acetyl Salicylic Acid, PC1 = Platelet count prior to anagrelide therapy; PC2 = Platelet count during anagrelide therapy. R = Response to therapy: CR Complete Response, HU & A = dosage of hydroxyurea and anagrelide in combination when platelet counts were reduced, AD= Adverse effects (H = Headache, P = Palpitations, T = Tachycardia, FR = Fluid Retention), D = Duration of therapy (months), DC = reason of discontinuation (PW = Patient Wish, BMT = Bone Marrow Transplantation, OMF = Osteomyelofibrosis, BC = Blast Crisis, D = Death) \* = platelet count dynamics shown in Figure 1.

No.	Age	Sex	Pretreatment	S	ASA	PC1	PC2	R	HU(g)	A (mg)	AD	D	DC
1*	46	M	HU	-	-	3300	583	CR	1,0	2,0	-	16	BMT
2	73	M	HU	-	-	1800	350	CR	2,0	2,0	-	23	OMF
3	67	F	HU	M	-	1400	295	CR	0	1,5	-	38	
4*	65	M	IF, HU	M,B	-	1500	278	CR	1,5	1,0	-	18	BC
5	57	M	HU & IF, HU	T,M	+	1300	427	CR	1,75	2,0	P,T	30	
6	53	F	BU, HU	M	-	976	280	CR	1,25	3,0	-	22	
7*	55	F	IF, HU	M	-	1250	401	CR	0	2,0	-	31	
8*	63	F	IF, HU	M,T	+	1550	300	CR	1,5	1,0	H	8	BC
9	52	F	IF, HU	-	-	2030	215	CR	2,5	1,75	FR	1	BC
10	60	M	HU	-	-	3400	247	CR	3,5	2,0	-	16	
11	57	M	IF, ME, HU	B	+	2100	606	CR	1,0	3,0	-	6	PW
12	50	M	IF, HU	-	-	3600	230	CR	1,5	1,5	-	5	D



**Figure 1.** Platelet count dynamics in four patients with CML after initiation of anagrelide treatment

## RESULTS

### *Patient Characteristics*

The median age of our twelve patients at the initiation of anagrelide therapy was 58 years (Table 1). Five patients were women and seven men. All twelve individuals were on treatment with hydroxyurea; some of them had obtained previously interferon- $\alpha$ , melphalan or busulfan. Three of 12 also obtained acetylsalicylic acid as an adjunct. The median platelet count before the initiation of anagrelide therapy was about 2,000,000/ $\mu$ l. Seven of 12 were symptomatic because of elevated platelet counts and had either microcirculatory disturbances, thrombosis or bleeding.

### *Hematological Response to Therapy*

Platelet count reduction occurred in all patients. Since response was defined as reduction of the platelet count to less than 600,000/ $\mu$ l or less than 50% of the original value, all patients

were responders. Median dosage required to maintain this level for a period of at least four weeks was 1.9 mg/day. The dynamics of the platelet decrease in 4 patients (Patients 1,4,7 & 8) are illustrated in Figure 1. Symptoms due to elevated platelet counts disappeared in all seven patients. In 8/12 patients the hydroxyurea dosage could be reduced, in two patients discontinued after the reduction of the platelet count with anagrelide.

Side effects typical for anagrelide application were seen in three patients, i.e. headache (1), tachycardia (1), palpitation (1) and fluid retention (1). No additional adverse effects due to the combination of anagrelide with hydroxyurea were observed, however.

At present 5 of the 12 patients remain under treatment with anagrelide (median duration of treatment 11 months). Reasons for discontinuation of therapy in the other patients were bone marrow transplantation (Patient 1), osteomyelofibrosis (Patient 2), blast crisis (Patients 4, 8 & 9), patient's request (Patient 11) or death (Patient 12).

## DISCUSSION

Bleeding and thrombotic complications are the typical symptoms in patients with myeloproliferative disorders with high platelet counts including CML where they can contribute to the morbidity in up to 25% of the patients (5,6,7). In CML thrombocytosis is either observed at presentation (8) or can develop during the distinct phases of the disease. In an analysis from a single US institution (NCI, Bethesda) two thirds (71/111) of CML patients presented with elevated platelet counts ( $> 450,000/\mu\text{l}$ ) either at diagnosis (56 = 50%) or in the subsequent course of the disease (15 = 14%) (9). Twenty-nine of the 71 had platelet counts in excess of  $1,000,000/\mu\text{l}$ . In this group four individuals had serious thrombohemorrhagic complications such as priapism, massive retroperitoneal hematoma or intracranial hemorrhage. In another large cohort of patients (M.D.Anderson, Houston) 47 of 830 (= 6%) patients developed platelet counts of more than  $700,000/\mu\text{l}$  during chronic phase which increased to 34/191 (= 18%) in accelerated and 25/109 (= 23%) in blast phase (10). In an investigation from the Hammersmith Hospital in London one third of the CML patients had platelet counts of more than  $600,000/\mu\text{l}$  (11). The British patients had no ischemic complications which may be due to their age (two thirds younger than 40) since they were referred to this center for allogeneic bone marrow transplantation.

Patients in our series were older (from 46 to 73 years) so that only one of them underwent bone marrow transplantation. Eight of 12 had marked thrombocytosis with platelet counts of more than  $1,500,000/\mu\text{l}$  and seven were symptomatic (microcirculatory disturbances, thrombosis or bleeding) so that platelet count reduction was indicated.

Since all of them were already receiving hydroxyurea treatment only a further increase of the dosage could have led to a reduction of the platelet count. This can often not be achieved because the megakaryocytes have become drug

resistant or only be achieved with high doses which cause anemia and leukocytopenia. Previously such a thrombocytosis was then treated with either interferon- $\alpha$  (12), thrombocytopheresis (13) or intravenous thiotepea (14).

Since some of our patients had already received interferon- $\alpha$  before and the effect of thrombocytopheresis is only of short term nature we decided to evaluate the efficacy of anagrelide in this situation. Anagrelide is a novel platelet-reducing agent that has been shown to be effective in the control of primary thrombocytopenia (3,4). We therefore added this drug to hydroxyurea in patients who developed high platelet counts. Our results in twelve patients with CML and a high platelet count show that the combination of hydroxyurea and anagrelide easily controls elevated platelet counts in all twelve patients. None of our patients developed side effects due to the combination of the two drugs.

Because the platelet counts could be efficiently controlled in all our patients and symptoms due to elevated platelet counts disappeared in all symptomatic patients, the use of anagrelide in such a situation may improve their quality of life by reducing or preventing thrombohemorrhagic complications.

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