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Interferon Alpha-2a to Control Thrombocytosis in Chronic Myelogenous Leukemia and Essential Thrombocythemia

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SUMMARY **Four patients with chronic myelogenous leukemia and thrombocytosis and one patient with essential thrombocythemia were treated with purified recombinant human interferon alpha-2a (IFN-α 2a). Significant decline in platelet counts, from a mean (± SE) of 1.396 ± 0.265 × 10^6/mm^3 to a mean of 0.396 ± 0.04 × 10^6/mm^3 ($p < 0.05$), was observed in all patients. The platelet count remained normal for 15, 21 and 30 days after discontinuation of IFN-α 2a in 3 patients. In 2 patients the platelet count began to rise slowly two weeks after discontinuation of IFN-α2a. Our preliminary observations suggest that purified recombinant human IFN-α 2a may effectively control progressive thrombocytosis in advanced chronic myelogenous leukemia and essential thrombocythemia.**

Interferons have opened new possibilities for the management of patients with cancer. Human alpha interferon (IFN-α) is produced by virus stimulated leukocytes and it has undergone extensive trials which have shown promising results in several tumors including hairy cell leukemia and renal cell cancer.[1,2] The activity of IFN-α in chronic myelogenous leukemia (CML) has also been documented.[3-5] Concommitant with the marked decline in leukocyte counts among the responding patients, a significant decrease in the peripheral blood platelet count was also observed.[4] It has also been shown that IFN-α is effective in selective reduction of platelet counts in patients with essential thrombocythemia.[6] This prompted a study of four patients with chronic myelogenous leukemia whose primary problem was thrombocytosis and one patient with essential thrombocythemia that failed to respond adequately to chemotherapy.

PATIENTS AND METHODS

Four patients with Philadelphia chromosome-positive chronic myelogenous leukemia and thrombocytosis ($\geq 0.6 \times 10^6$/mm^3) and one patient with essential thrombocythemia were studied. The group studied consisted of three males and two females with ages ranging from 25 to 68 years. The disease had been present for 6 months to 4 years before the study began (median, 2 years). Two patients were treated with busulfan 2 mg daily and two patients were treated with 6 thioguanine 80 mg daily. The other patient was given busulfan 2 mg weekly. In 4 patients, the leukocyte count was either normal or slightly decreased which precluded further increases in the chemotherapy dose. The platelet count in all 5 patients increased despite the chemotherapy.

Before the study, all patients had complete blood counts done, liver and renal functions were assessed; serum calcium, uric acid, and electrolytes were measured. During the study, complete blood counts were repeated every day and the blood chemistry tests were done once a week. Statistical analysis of the change in the mean platelet count was done with the Wilcoxan Signed Ranks test. Purified recombinant human interferon alpha-2a with a specific activity of 3×10^6 units/ml was used (Roferon® , Roche, Basel, Switzerland). All patients received 3×10^6 units of human interferon alpha-2a daily by subcutaneous injection.

RESULTS

The clinical course of the patients after treatment with purified

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Table 1. Clinical course of patients with chronic myelogenous leukemia and essential thrombocythemia treated with purified recombinant human interferon alpha–2a

Patient	Change in Platelet count ($\times 10^6/mm^3$)		Time to platelet count of less than $0.6 \times 10^6/mm^3$ (day)	Time to 50% Reduction in Platelet count (day)	Change in leukocyte counts ($\times 10^3/mm^3$)		Duration of therapy (day)
	Pretherapy	End of therapy			Pretherapy	End of therapy	
1	1.896	0.263	9	3	11.9	3.4	6
2	2.177	0.404	11	4	7.9	6.0	16
3	0.981	0.482	7	5	8.0	9.3	6
4	0.983	0.40	10	11	20.3	6.62	41
5	0.943	0.434	3	6	5.47	4.425	6
Mean ± SE	1.396 ± 0.265	0.396 ± 0.04	8.00 ± 1.41	5.8 ± 1.39	10.714 ± 0.26	5.95 ± 0.01	15 ± 6.78

recombinant human interferon alpha-2a is shown in Table 1. A significant decrease in the platelet counts, from a mean of $1.396 \pm 0.265 \times 10^6/mm^3$ to a mean of $0.396 \pm 0.04 \times 10^6/mm^3$ ($p < 0.05$) was seen. The mean time for a 50 percent reduction in platelet count was 5.8 days. Neither thromboembolic nor hemorrhagic complications occurred during the study. In contrast to the significant decrease in the platelet count, purified recombinant human interferon alpha-2a had no significant influence on peripheral leukocyte count. The platelet count remained normal for 15, 21 and 30 days after discontinuation of interferon in 3 patients. In 2 patients, the platelet count began to rise slowly two weeks after cessation of interferon. All 5 patients experienced mild side effects from interferon including low grade fever (usually $< 38°$ C), mild muscle pain and malaise. These symptoms disappeared after the discontinuation of interferon.

DISCUSSION

Thrombocytosis is common among patients with chronic myelogenous leukemia, occurring at the onset or later during the course of the disease.[7] It can be present clinically as thromboembolic and hemorrhargic phenomena.[7,8] The incidence of these complications may have been underestimated in the past. In our series of 94 patients with chronic myelogenous leukemia, about 62 percent developed thrombocytosis of greater than $0.6 \times 10^6/mm^3$ and in 33 percent of the patients, the platelet counts were greater than 1×10^6 mm^3 (unpublished observation). The peripheral blood granulocyte count can usually be controlled with chemotherapeutic agents, however, the control of the thrombocytosis is sometimes quite difficult, and occasionally the platelet count continues to rise despite the continuation of chemotherapy. Human leukocyte interferon alpha appeared to be effective in controlling the thrombocytosis without any significant reduction in the peripheral blood leukocyte count.[9] It is interesting that the leukocytes and platelets respond differently to chemotherapy and interferon. The leukocytes were more sensitive to the chemotherapy whereas the platelets were more sensitive to the cytoreductive effect of the interferon. Therefore a proper combination of these treatment might be useful in controlling chronic myelogenous leukemia at this stage.

Human leukocyte interferon alpha is quite expensive in comparison with busulfan or 6 thioguanine. For a developing country, oral chemotherapy like busulfan or 6 thioguanine is still both effective and economical for most patients with chronic myelogenous leukemia and essential thrombocythemia. However, in selected patients with CML and thrombocytosis despite chemotherapy and a near normal or slightly decreased leukocyte count which precludes further increase in chemotherapy, human leukocyte interferon alpha appears very promising for control of thrombocytosis.

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