The pattern of fetal hemoglobin changes in patients with malignancy on chemotherapy

Caroline E. Omoti, *MBBS, FMC Path,* ***Evarista O. Osime,*** *AIMLT (Haem), FIMLT (Microbiology),*
Casmir E. Omuemu, *MBBS, FWACP.*

ABSTRACT

Objectives: Production of fetal proteins by malignant tissue is a recognized phenomenon seen in many neoplastic disorders. Hence, the aim was to determine if there is a positive correlation between administration of chemotherapy and reduction in fetal hemoglobin (HbF) levels.

Methods: In a prospective study at the University of Benin Teaching Hospital, Nigeria, 50 cancer patients at various stages of the disease and 50 controls for 10 months period (March to December, 2005), HbF was determined in pre-chemotherapy (n=23) and post-chemotherapy (n=27) cancer patients. Fetal hemoglobin was estimated by the modified Betke's method.

Results: A total of 20 patients (40%) comprising 10 pre-chemotherapy and 10 post-chemotherapy patients presented with increased HbF which was statistically significant ($p<0.0001$). There was also a significant decrease in post-chemotherapy result when both pre and post-chemotherapy values were compared ($p=0.0073$).

Conclusion: The results presented indicate that during recovery of erythropoiesis some erythroblasts synthesized HbF and there was a reduction following administration of chemotherapy.

Saudi Med J 2006; Vol. 27 (10): 1523-1525

Fetal hemoglobin (HbF) is the predominant form of hemoglobin produced during fetal life. This is replaced with the adult hemoglobin molecule in the postnatal life and it account for not more than 1.5% of the total adult hemoglobin depending on the region.[1,2] Several genetic factors have been reported to control HbF production.[3-5] Production of fetal proteins by malignant tissue is a recognized factor seen in many neoplastic disorders.[6,7] It is difficult to arrive at any significant conclusion regarding the need and the mechanism for the switch over from adult hemoglobin to HbF in different disorders. There is evidence to suggest a reversion to production of adult hemoglobin on remission of the cancer following chemotherapy but data on this is still grossly limited. Hence, the purpose of this study was to record the HbF levels in cancer patients in our environment, which has not been carried out previously and determine if there is a positive correlation between administration of chemotherapy and reduction in HbF levels.

Methods. One hundred subjects aged ≥18 years in a prospective study at the University of Benin Teaching Hospital, Nigeria was studied over a 10 months period (March - December 2005) after informed consent. This comprised 16 (32%) hematological malignancies, 34 (68%) non-hematological malignancies and 50 controls that were prescreened and found without any history

From the Department of Hematology (Omoti, Osime) and the Department of Medicine (Omuemu), University of Benin Teaching Hospital, Benin City, *Nigeria*.

Received 7th March 2006. Accepted for publication in final form 21st June 2006.

Address correspondence and reprint request to: Dr. Caroline E. Omoti, Department of Hematology, University of Benin Teaching Hospital, PMB 1111, Benin City, *Nigeria*. Tel. +234 (805) 6014028. E-mail: ediomoti@yahoo.com

of malignancy or any disorder. The inclusion criteria were based on presence of typical clinical features and specific diagnostic criteria for the various cancers. All the tests were carried out prior to any form of blood transfusion on pre and post-chemotherapy patients on cytotoxics drugs after an average of 4 cycles. Fetal hemoglobin was estimated by the modified Betke's et al[8] method while the hematological parameters (hemoglobin, total leucocyte count, platelets and erythrocyte sedimentation rate [ESR]) were obtained by standard methods. Reference value for HbF in our laboratory ranged from 0.1-1.5% and any rise above this level was considered abnormal. Differences in HbF levels and hematological values were estimated by the Mann-Whitney test. GraphPad (instat) Version 2.05a statistical software was used in data analysis.

Results. A total number of 100 subjects at the time of study (March to December 2005) comprised 23 pre-chemotherapy patients comprising 18 males and 15 females, 27 post-chemotherapy patients comprised 11 males and 16 females and 50 controls comprised 24 males and 26 females. The mean age was 46.5 ± 15.4 with a peak age incidence in the 5th decade of life. Thirty patients with malignancy had HbF levels within normal limits (0.1-1.5%) while 20 patients (40%) presented with increased HbF (between 1.6- 4.1%), which was significant (p<0.0001).

Table 1 shows the mean (±SD) fetal hemoglobin and hematological values comparing the controls, pre, and post-chemotherapy cancer patients respectively. From our study the pre and post-chemotherapy hemoglobin (Hb) values decreased significantly (p=0.006 versus p<0.0001) while the ESR increased significantly (p<0.0001) when compared with the controls. Although the total leucocyte count was significantly higher than the controls, it was still within the normal range (4-11,000/mm^2). There was a decrease in platelet counts in both pre and post-chemotherapy patients, although this was not significant and the counts were within the normal range (100-400,000/mm^2). Only the drop in Hb and HbF values were statistically significant when pre and post-chemotherapy values were compared (**Table 1**).

Discussion. Investigation of fetal hemoglobin (HbF) in malignant disorders has shown it to be significantly raised in a number of benign or malignant acquired hematological disorders.[6,7] It has been postulated that in patients with malignant disease, a humoral factor is produced which interferes with normal erythropoiesis resulting in a reversal of differentiation.[9] Majority of the patients (60%) at the time of diagnosis had an Hb level of less than 10g/dl. This is not surprising because anemia has been shown to be a common finding among cancer patients. The probability of occurrence of anemia depends on a well-defined number of variables.[10] This decrease in Hb may largely be due to the toxic nature of the chemotherapeutic agents as well as disease entity

Table 1 - Hematological and fetal hemoglobin values in controls, pre-chemotherapy and post-chemotherapy patients.

Variables	**Pre-chemotherapy (n=23)**	**Controls (n=50)**	***P* values**
Hemoglobin (g/dl)	11.62 ± 2.26	12.46 ± 1.47	0.006
Total leucocyte count (x10^9/l)	10.2 ± 6.0	5.10 ± 1.9	0.0001
Platelet count (x10^9/l)	170 ± 8.0	202 ± 61	ns
ESR (mm/hr)	74.3 ± 36	14.9 ± 7.3	0.0001
Fetal hemoglobin (%)	1.71 ± 0.7	1.1 ± 0.2	0.0001
	Post-chemotherapy n=27)	**Controls (n=50)**	***P* values**
Hemoglobin (g/dl)	9.7 ± 2.4	12.46 ± 1.47	0.0001
Total leucocyte count (x10^9/l)	8.9 ± 7.5	5.10 ± 1.9	0.001
Platelet count (x10^9/l)	186 ± 90	202 ± 61	ns
ESR (mm/hr)	74.2 ± 34	14.9 ± 7.3	0.0001
Fetal hemoglobin (%)	1.23 ± 0.5	1.1 ± 0.2	0.0002
	Pre-chemotherapy	**Post-chemotherapy**	***P* values**
Hemoglobin (g/dl)	11.62 ± 2.26	9.7 ± 2.4	0.0057
Total leucocyte count (x10^9/l)	10.2 ± 6.0	8.9 ± 7.5	ns
Platelet count (x10^9/l)	170 ± 80	186 ± 90	ns
ESR (mm/hr)	74.3 ± 36	74.2 ± 34	ns
Fetal hemoglobin (%)	1.71 ± 0.7	1.23 ± 0.5	0.0073

Data are expressed as mean (±SD), ns - not significant, ESR - erythrocyte sedimentation rate

itself causing a decrease in hemopoesis[11] and other side effects. Thrombocytopenia is usually found in the late stages of disease while the total leucocyte counts though statistically increased when compared to controls was still within the normal levels. Also, all the patients presented with an elevated ESR of >50mm/hr at the time of diagnosis with only a slight decrease post-chemotherapy and this is in agreement with other studies.[12,13] Elevation of the ESR is most common with advanced disease and reveals aggressive nature of the disease. This increase could be due to the reduction in Hct and alteration in serum proteins especially fibrinogen. The occurrence of elevated HbF value in 40% (20 cases) was significant in pre (p<0.0001) and post-chemotherapy patients (p=0.002). The incidence of occurrence of high HbF values was variable in different malignancies. The highest value was seen in Hodgkin's lymphoma with a value of 4%, which is in contrast to the 35.4% recorded for chronic myelogenous leukemia (CML) in another study.[6] In half of the cases where HbF was estimated post-chemotherapy after induction of a remission the amount of HbF was found to have increased which was in contrast to the significant decrease in HbF levels post-chemotherapy in this study (p=0.0073). This was similar to another study where 8 out of 9 patients with increased HbF had a decrease HbF in remission post-chemotherapy.[14] Therefore, there is no obvious clinical or laboratory feature to predict alteration in HbF level and its clinical significance remains obscure. Some of the cases revealed raised HbF as an effect of rapid regenerative process occurring after aplasia due to the treatment with cytotoxic drugs. Interestingly, in a similar study it was concluded that only CML is characterized by acquired rise in HbF.[15] However, the finding in this study is different as Hodgkin's lymphoma, other cancers had increased HbF, and greater decrease was observed in those achieving a clinical remission. The levels of HbF usually declined during remission but high levels persisted in a few cases.

In conclusion, this study demonstrates that in patients with high HbF, chemotherapy led to significant drop in the HbF levels. Thus, a drop in previously high HbF levels may be a useful tool for monitoring response to chemotherapy.

References

1. Kotila TR, Shokunbi WA. Haemoglobin F levels in healthy Nigerian adults. ***West Afr J Med*** 2003; 22: 143-145.
2. Sergeant GR. Sickle cell disease. New York: Oxford University Press New York; 1985. p. 34-83.
3. Dedoussis GV, Sinopoulou K, Gyparaki M, Loutradis A. Fetal hemoglobin expression in the compound heterozygous state for -117 (G-->A) Agamma HPFH and IVS-1 nt 110 (G-->A) beta+ thalassemia: a case study. ***Eur J Haematol*** 2000; 65: 93-96.
4. Trachoo O, Sura T, Sakuntabhai A, Singhasivanon P, Krudsood S, Phimpraphi W et al. Molecular characterization of hereditary persistence of fetal hemoglobin in the Karen people of Thailand. ***Hemoglobin*** 2003; 27: 97-104.
5. Garner C, Silver N, Best S, Menzel S, Martin C, Spector TD et al. Quantitative trait locus on chromosome 8q influences the switch from fetal to adult hemoglobin. ***Blood*** 2004; 104: 2184-2186.
6. Agarwal MB, Mehta BC, Rao SS. Raised foetal haemoglobin in haematological malignancies. ***J Postgrad Med*** 1983; 29: 15-19.
7. Zhou L, Liu J, Luo F. Serum tumor markers for detection of hepatocellular carcinoma. ***World J Gastroenterol*** 2006; 12: 1175-1181.
8. Dacie JV, Lewis SM. Investigation of abnormal haemoglobins and thalassaemia. Practical Haematology. 8th ed. Edinburgh: Churchill Livingstone; 1994. p. 249-286.
9. Barton J, Cauchi MN. F cells in gynaecologic malignancy. ***Gynecol Obstet Invest*** 1979; 10: 205-211.
10. Ludwig H, Rai K, Blade J, Dammacco F, Degos L, Itri L et al. Management of disease related anaemia in patients with multiple myeloma or chronic lymphocytic lymphoma: epoetin treatment recommendations. ***Haem J*** 2002; 3: 121-130.
11. Thompson RB, Proctor SJ. A short textbook of Haematology. 6th ed. Honking: Longana Group Limited; 1984. p. 416-450.
12. Olshaker JS, David AJ. The erythrocyte sedimentation rate. ***The Journal of Emergency Medicine*** 1997; 11: 867-870.
13. Cheesbrough M. District Laboratory Practice in Tropical countries. United Kingdom: Cambridge University Press. 1992; p.341-345.
14. Pribilovic D, Pavlovic-Kentera V. Fetal haemoglobin in the blood in leukemia. ***Bilt Hematol Transfuz*** 1980; 8: 65-70.
15. Sheridan BL, Weatherall DJ, Clegg JB, Pritchard J, Wood WG, Callender ST et al. The patterns of foetal haemoglobin production in leukemia. ***Br J Hematol*** 1976; 32: 487-506.