Severe depression following á-interferon usage in a patient with chronic myeloid leukemia

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Abstract

Background:

Chronic myeloid leukaemia (CML), with a median age of 40 years, is one of the commonest haematological malignancies in Nigeria. Cytoreductive agents, which were hitherto to the mainstay of treatment, neither induce cytogenetic nor haematologic remission. Alpha-interferon (á-IFN), an endogenous glycoprotein with cytotoxic and natural killer cell enhancer effects has been found to induce haematologic and cytogenetic remission in patients with CML, but neuro- psychiatric complications of á -interferon (á-IFN) usage were not reported in Nigeria.

Objective: To report a case of deliberate self-harm in University Lecturer as a side effect of á-IFN in the treatment of CML

Method: Clinical and laboratory follow up of a patient receiving á-IFN in the management of CML from the time of diagnosis of CML to the point of loss of contact.

Result: Severe depression is a complication that may adversely influence the clinical outcome of á-IFN usage

Conclusions/Recommendations: Although interferon related depression is uncommon, it is suggested that pre-therapy interferon assays and neuro-psychiatric assessment are carried out in prospective users of á-IFN

Key words : Chronic myeloid leukaemia, interferon-á, depression

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Introduction

Chronic myeloid leukaemia is a Multistep myeloproliferative disorder characterised by granulocytic leucocytosis.[1,2] The earliest or chronic phase is found in 85% of patients. The Philadelphia (Ph^1) chromosome is the most common cytogenetic anomaly, whose mutant BCR-ABL fusion gene codes for a 210 KD hybrid protein that is the hallmark of the disease, and is found in 95% of cases.[2] Interferon reduces the survival of leukaemic cells thus decreasing the amplification of secondary colonies in CML.[2] It also induces haematological and cytogenetic remission by activating Natural Killer cells and the repression of oncogenes.[3-5] Numerous investigators have reported prolonged survival after cytogenetic response in persons following the use of α-IFN.[4-7] IFN-á has also been used in the treatment of viral hepatitis, multiple myeloma and Non-Hodgkin's Lymphoma.[6] Side effects of IFN are flu-like syndrome characterised by headaches, fever, myalgia, arthralgia, neuropathy, amnesia, depression, psychosis, confusion, convulsion and coma.[7-12] Cytokine activation, alterations in stress hormone release and serotonin reuptake are the mechanisms of interferon-induced depression.[10-12] Interferon induced depression may be related to observed elevation in the levels of endogenous interferon in some psychotics.[11] Treatment of interferon-induced depression entails the use of antipsychotics and antidepressants.[11] Non Steroidal anti-inflammatory drugs (NSAIDS) like acetylsalylic acid have the potential of preventing and treating interferon-induced depression irrespective of background psychopathology.[11]

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Case Report

A venous blood sample sent to our laboratory for the complete blood count from PBD a 42 year old University Lecturer as part of investigation for typhoid fever revealed a markedly leucocytic film with a count of 193 $x10^9$/L. The platelet count was 168 $x10^9$/L. The predominance of myelocytes, metamyelocytes, band forms, and mature forms and a preliminary diagnosis of chronic myeloid leukaemia (CML), in chronic phase, prompted a search for the patient to whom the blood sample belonged. The patient was found 9 days later by which time the leucocyte count had risen to 314$x10^9$/L. The haematocrit was 29L/L. Initial assessment revealed a febrile gentle man of the Roman Catholic faith, with an anxious countenance, mild pallor who had

a splenomegaly of 12 cm below the left hypochondrium, with scrotal tenderness but no areas of fluctuance. The respiratory and cardiovascular systems were normal. A bone marrow aspirate was taken to exclude the accelerated and blastic transformation phases of CML as we lack the capacity for cytogenetics and neutrophil alkaline phosphatase detection. The hypercellular aspirate showed myeloid hyperplasia, with bimodal peaks at the myelocyte and mature neutrophil stages. While the megakaryocytes were increased, the blasts accounted for less than 5% of nucleated bone marrow cells. This confirmed the diagnosis of chronic phase CML. Pre-treatment á-interferon activity was not done. Blood chemistry was normal. Patient was counselled on the implications of diagnosis and treatment options, after which Busulphan at a daily dose of 6mg was commenced for six weeks. Improved access to funds facilitated the procurement of á-interferon as it proffered cytogenetic remission contrary to the cytoreductive effects of Busulphan though side effects like alopecia were common to both.

Therapy with á-interferon (á-IFN) was commenced at a dose of 9MU subcutaneously daily six weeks after diagnosis was made and the leucocyte count was 171.5 $x10^9$/L. The patient reported effects like myalgia, fever and body weakness which lasted three weeks. This was managed with acetylsalicylic acid tablets.

Five weeks into á-IFN usage, alopecia with grey patches were observed but the splenomegaly and leucocyte count progressively decreased. Normal leucocyte counts were restored in the fourth month. In the fifth month of á-IFN usage, the patient was observed to be sleeping poorly, withdrawn and frequently expressed suicidal ideation. His wife described him as intelligent, sociable but became superstitious at the onset of the illness. There is neither a contributory past medical history nor a family history of depressive illness.

The mental state assessment revealed a withdrawn young man who was appropriately dressed and well groomed. He was withdrawn and looking down cast. He described his mood as that of sadness and had a depressed affect. His speech is low tone and barely audible. He was preoccupied with the thought of death and believed that he was better dead than alive.

Historical findings strongly point toward a paranoid premorbid personality with a tendency towards projected aggression.

Physical examination revealed a healthy looking man who was mildly pale, anicteric and a sutured horizontal laceration of the right wrist. The laceration followed a razor blade slash of the wrist. The cardiovascular and respiratory systems were essentially normal. The spleen was 4cm below the costal margin with a tipped liver mass. Clinical features of acceleration and /or blastic transformation like bone pain and tenderness, stigma of haemorrhagic disorders like muco-cutanous haemorrhage were absent, while the total leucocyte count was $18x10^9$/L. Based on this a diagnosis of á-interferon induced severe depression was made in a patient who was still in the chronic phase of CML. Although the patient had insight into his problems, he lamented the hopelessness associated with having leukaemia in a Nigerian community with very young children.

Psychiatric management entailed stoppage of á-interferon, and its substitution with hydroxyurea at dose 1.5g per day. He also received 6 shots of electro-convulsive therapy

His mental state improved 3 weeks after commencement of psychiatric management and resumed his normal activity. He remained stable for five years and was subsequently lost to follow up.

Discussion

The diagnosis of CML was made accidentally in course of investigations for typhoid fever which is of Public Health significance in Nigeria.[13] Accidental diagnosis accounts for 50% of CML diagnosis. [14]Our patient's age and mode of presentation in the chronic phase of CML are comparable to 85% of cases reported by Stefan Faderl and colleagues.[2] Although the common features of CML like anaemia, splenomegaly, bone tenderness and priapism were absent in our patient, scrotal pain are uncommon features that have been reported in some patients with Acute Myeloid Leukaemia which contrasts with the diagnosis in our patient.[15] A morphology based diagnosis of CML confirms the observation by Stefan and colleagues that at least 50% of CML cases are diagnosed routinely.[2] The absence of cytogenetic studies and the initial choice of Busulphan an alkylating agent reflect infrastructural inadequacy plaguing most developing countries. Ph^1 positive CML is found in 90-95% of cases. This prompted the choice of á-IFN in which improved survival with rapid response, due to varying degrees of cytogenetic and haematological remission has been reported. [5-9] This suggests that IFN-á is superior to conventional cytoreductive agents like Busulphan, and Hyroxyurea as IFN-á confers a 3 year and 10 year survival rate of 76% and 30%respectively.[5]This contrasts with 18% observed in persons who received conventional chemotherapy for 10 years.[5]Wandl reported a complete cytogenetic response rate of 11%, and a partial response rate of 43%, with a non-response observed in 6 patients following the combined usage of IFN-á and low dose recombinant IFN-ã in patients previously treated with chemotherapy. [9] Although our patient had prior chemotherapy, he only received IFN- á for less than a year. This is shorter than the duration of á-interferon usage in the patient reported by Durosinmi and colleagues.[16] Initial side effect reported by our patient was the flu-like syndrome

characterised by myalgia, arthralgia, and fever in the early days of commencement of treatment for which a short course of non-steroidal anti-inflammatory acetylsalicylic acid was administered. Although the use of acetylsalicylic acid in our patient was restricted to the management of the flu like syndrome, Asnis and team recommend that acetylsalicylic acid may also be used for the prevention and treatment interferon related depression.[11] Depression observed in our patient is comparable to reports by Martee Hensley et al, though our patient had no prior history of either neurological illness or depression. But the emergence of depression in the fifth month of commencing á-interferon is similar to the report by Mahon team in which depression due to á-interferon usage was a reason for cessation interferon usage in CML.[11] Tamam et al have also reported the emergence of interferon induced depression in a patient in the 5th month of therapy.[11] Although elevated serum interferon levels have been observed in persons with psychosis, neither serum nor cerebrospinal fluid interferon was assessed in our patient reflecting our infrastructural limitations. The Naranjo probability scale for determining the role of interferon in depression cannot be applied in this case as spectrophotometric á-IFN assay was not done.[10] Satisfactory haematological and cytogentic response in Nigerian patients on alpha interferon reported by Okanny et al is limited by life-threatening cytopaenias.[6] Whereas á-interferon prolongs life with an accelerated haematological remission, its use in our settings calls for strengthening of existing infrastructure with emphasis on cytogenetics, interferon assays, pre-treatment psychiatric assessment, transfusion and transplantation support.

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