Survival of twenty-two months in a patient with primary plasma cell leukaemia treated with melphalan and prednisolone

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Summary: In the majority of cases plasma cell leukaemia is a rapidly fatal disease with a mean survival time of five months. There have been reports of increased survival using various regimens of chemotherapy although most cases eventually relapse.

We describe a patient with primary plasma cell leukaemia who responded to a combination of oral melphalan and prednisolone with control of the disease in the bone marrow but relapsed with extramedullary disease in the central nervous system and testes, and died 22 months after diagnosis.

Melphalan poorly penetrates the central nervous system and its testicular penetration is unknown.

Introduction

Plasma cell leukaemia as defined by an absolute plasma cell count of greater than 2×10^9 /litre in the peripheral blood or more than 20% of the peripheral leucocytes as plasma cells¹ may occur in patients already suffering from multiple myeloma (about 2% will develop this complication) or may be the first presentation of a plasma cell malignancy, so-called primary plasma cell leukaemia. This is a rare condition with 49 cases reported between 1965 and 1980.¹ The mean survival time between diagnosis and death is 4.9 months, although three complete remissions have been reported.^{1,5,6}

A number of treatment regimens have been suggested,^{1,2,5-16} including the conventional therapy for multiple myeloma of melphalan and prednisolone,^{2,6,7,15,17,18,26} but no single regimen has yielded consistent remissions.

We describe a patient with primary plasma cell leukaemia treated with cyclical courses of oral melphalan and prednisolone effecting control of the disease in the bone marrow and an initial excellent clinical response, only to relapse with leukaemic deposits in his testes and central nervous system 14 months after diagnosis. At that time there was no objective evidence of active disease in the bone marrow.

In this case the central nervous system and testes may have acted as sanctuary sites from the effect of the chemotherapy as is seen in cases of acute lymphoblastic leukaemia in children.²³

Case report

In November 1984 a 62 year old Caucasian male was admitted with a 6 week history of lethargy, weakness and dyspnoea on exertion. On examination he was clinically anaemic with no other abnormalities.

Investigations revealed: haemoglobin 7.8 g/dl, MCV 95.7 fl, white cell count 13.8×10^9 /l, neutrophils 19%, lymphocytes 39%, monocytes 1%, eosinophils 2%, plasma cells 38%, platelets 100×10^9 /l. The erythrocyte sedimentation rate was 146 mm/h. There was a monoclonal IgG ((lambda) serum paraprotein (52 g/l) with lambda Bence-Jones proteinuria. Blood urea and calcium, and skeletal X-rays were normal.

Bone marrow examination from a sternal aspirate revealed a hypercellular marrow virtually replaced by sheets and clumps of plasma cells some of which were well differentiated but many were larger and primitive. Erythropoiesis and myelopoiesis were both very depressed and only an occasional megakaryocyte was identified.

The initial management consisted of a blood transfusion, allopurinol 300 mg/day and courses of melphalan 15 mg/day and prednisolone 45 mg/day

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for 5 days every 3 weeks. He made an excellent clinical, haematological and biochemical response. After eight courses of treatment the interval between courses was increased to three months and he received a final course in March 1986, when the serum IgG concentration was 6.9 g/l and his marrow contained 3% plasma cells.

In December of 1985 he suffered a vitreous haemorrhage destroying the sight of his right eye and in February 1986 he gave a 5 week history of tenderness and swelling of the testes. Biopsies revealed testicular tissue replaced by plasma cells and he underwent bilateral orchidectomy.

In April 1986 he gave a 2 week history of deteriorating hearing and on examination he had bilateral neuronal deafness, bilaterally decreased corneal reflexes and a left lower motor neurone seventh nerve lesion. Examination of his cerebrospinal fluid revealed bloodstained fluid and a protein content of 800 mg/dl. Plasma cells were seen and an IgG paraprotein was isolated. A computed tomographic (CT) brain scan showed multiple enhancing deposits in both cerebral hemispheres (Figure 1).

Figure 1 Computerized axial tomogram demonstrating intra-cerebral tumour deposits. Abnormal plasma cells and the IgG paraprotein were isolated from the cerebrospinal fluid.

He received methyl prednisolone 1.5 g/day intravenously for 5 days with no clinical or CT improvement. He was given carmustine (BiCNU) 300 mg intravenously with no clinical improvement.

He died in September 1986, twenty-two months after diagnosis, following the development of retinal and subcutaneous deposits.

Discussion

Generally plasma cell leukaemia is rapidly fatal but there have been previous reports of a useful response to combinations of chemotherapeutic regimens.

Shaw *et al.*¹⁶ obtained a good partial response following a regimen of cyclophosphamide, vincristine, cytosine arabinoside and prednisolone (COAP) and later high dosage melphalan and prednisolone. Their patient survived for 13 months and Lishner *et al.*⁸ using COAP achieved a survival of 22 months.

Cyclophosphamide^{12,14} alone, or in combination with prednisolone^{12,13} has effected survival of up to 4 years and in one case doxorubicin successfully controlled subcutaneous tumour nodules. In our patient general debility precluded this being used. McElwain and Powles⁶ using high dose intravenous melphalan achieved a complete remission and their patient had a subsequent autograft of his remission bone marrow and one patient treated with ³²P had a prolonged remission only to die 12 years later in an accident.²

Generally the response of plasma cell leukaemia to conventional myeloma therapy of prednisolone and melphalan has been poor^{7,12} and only occasional remissions with this therapy have been reported. Pruzanski⁷ reported a patient surviving two years and Woodruff¹² a patient surviving 28 months, but most remissions, if they occur, are short lived,^{15,18,26} with a mean of 9 months.

The reason why certain patients respond to chemotherapy are not clear but it may be due to the degree of differentiation of the plasma cells.¹ If one accepts that the tumour grows exponentially a rapid response to treatment is a poor prognostic sign,²⁷ in that patients with multiple myeloma who showed a rapid response to treatment relapsed quickly and at two years after diagnosis only 39% survived compared to 78% surviving at two years who had shown a slow response. This may explain the reason for and nature of the relapse in this case.

There is good evidence from the bone marrow samples, peripheral blood counts and immunoglobulin levels that the treatment significantly reduced the tumour mass in the bone marrow, however there must have been at least as many

residual tumour cells in the bone marrow as seen in other acute leukaemias in remission. Similarly small numbers of tumour cells, not recognized in routine differential counts, may well have continued to circulate and these cells may have become trapped or homed-into the so-called sanctuary sites of the testes and central nervous system. These are recognized sites for deposits of plasma cell leukaemia^{9,12,17,28,32} and may occur despite a good clinical and haematological response to treatment.^{9,11,17}

There is an anatomical blood-brain barrier which is poorly penetrated by the use of intravenous melphalan^{19,20,21,22} and results in the brain acting as a sanctuary from chemotherapeutic attack. In acute lymphoblastic leukaemia specific measures are taken to attempt to control the disease process in the central nervous system. The response to local radiotherapy of intracerebral myelomatous deposits has been helpful³¹ but intrathecal methotrexate previously failed to control deposits of plasma cell leukaemia in the brain.¹²

It has been suggested that the lowered temperature of the testes in the scrotum creates a non-anatomical blood-testes barrier making this organ a sanctuary from chemotherapeutic attack and penetration of melphalan into the testes is unknown (personal communication, Wellcome Foundation). The treatment for plasma cell leukaemia deposits in the testes has been surgical.⁹

Achieving a response in plasma cell leukaemia with conventional therapy of melphalan and prednisolone is rare but if this occurs, extra-medullary relapses especially in sites protected from chemotherapeutic attack should be anticipated.

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