



Ibrutinib for a Paraneoplastic Polyneuropathy in Mantle Cell Lymphoma

Tucker DL*, Medd P, Hunter H and Rule S

Department of Hematology, Plymouth Hospitals NHS Trust, United Kingdom

Abstract

Mantle cell lymphoma is a rare and aggressive form of non-Hodgkin lymphoma. Paraneoplastic disease with central nervous system involvement is a rare complication. Immunosuppression for the paraneoplastic features and chemotherapy for the underlying malignancy are described treatments but benefits are often short-lived because of co-morbid complications and disease resistance. This report describes a case of relapsed MCL with a rapidly progressing, motor-dominant, paraneoplastic polyneuropathy treated with immunosuppression and ibrutinib, an inhibitor of Bruton's tyrosine kinase. Ibrutinib was well tolerated and led to a partial remission comparable in duration with that achieved by more toxic chemotherapeutic regimens, which are often difficult to deliver in this context. Paraneoplastic neurological syndromes are rare but recognized complications of mantle cell lymphoma which are important to diagnose because treating the underlying disease is an essential component of therapy. This report demonstrates that ibrutinib is a safe and effective therapeutic option.

Keywords: Ibrutinib; Mantle cell lymphoma; Central nervous system; Paraneoplastic syndrome; Anti-ganglioside antibodies

Introduction

Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma (NHL), genetically characterized by the t (11;14) chromosomal translocation resulting in over-expression of cyclin D [1] and deregulation of the cell cycle. It accounts for 4-10% of NHL with a median age at diagnosis of 68 years and an approximate 2:1 propensity for older males [2,3]. It often presents at a late stage and is generally regarded as incurable [4]. Median overall survival varies from 2 to 12 years and depends on several factors, including patient fitness for intensive therapy and disease features, such as the presence of blastoid histology [5,6]. Extra-nodal involvement is common: patients often present with blood, bone marrow and gastrointestinal infiltration [2,7,8].

Sensory, motor and autonomic neuropathies are a recognized complication of Hodgkin and non-Hodgkin lymphoma through a variety of mechanisms: leptomeningeal and parenchymal infiltration of the nervous system; metabolic disturbance; infection; complications of therapy and paraneoplastic syndromes [9-12].

Paraneoplastic neurological syndromes (PNS) are probably caused by immune mechanisms directed against self-antigens normally present in the central nervous system being ectopically expressed by the tumour (onconeural antigens). By definition, PNS occur in the absence of metastasis to or infiltration of the nervous system; known indirect toxic effect; ectopic secretion of hormones or induced coagulopathies. The frequency of PNS is low, occurring in <1% of patients with solid tumours [13]. They are rare in NHL but important to diagnose because treatment of the underlying tumour is an important initial step in their management [14-16].

There have been several reports of paraneoplastic neuropathies associated with immunoglobulin M (IgM) antibodies against the disialosyl gangliosides, including CANOMAD syndrome (Chronic Ataxic Neuropathy, Ophthalmoplegia, Monoclonal IgM protein, cold Agglutinins and Disialosyl antibodies) [17-23]. They are usually treated with a combination of plasma exchange (PEX) and immunosuppression in the form of corticosteroids, intravenous immunoglobulin (IVIg) or rituximab.

This article describes a rapidly progressing, motor-dominant polyneuropathy with IgM anti-ganglioside antibodies associated with relapsing MCL and its successful treatment with the Bruton's tyrosine kinase inhibitor, ibrutinib.

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*Correspondence:

David Tucker, Department of Hematology, Plymouth Hospitals NHS Trust, Derriford Road, Plymouth, PL6 8DH, United Kingdom, Fax: 01752 792400; Tel: 01752 432595; E-mail: david.tucker1@nhs.net

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Case Presentation

A 59 year old Caucasian male with a history of MCL treated four years previously with cytarabine-based chemotherapy followed by a reduced intensity, sibling-donor allogeneic stem-cell transplant, presented to a late-effects clinic with a four week history of dizzy spells. There was no previous history of neurological disorders. Clinical examination was unremarkable. A full blood count revealed a mild lymphocytosis ($5.1 \times 10^9/L$) with a population of blastoid lymphocytes on the blood smear. Immuno phenotyping of these cells demonstrated a MCL phenotype (CD5+; CD19+; CD79a+; FMC7+; CD20/22+; CD23-). Renal and liver biochemistry, including serum B12, folate and ferritin assays were normal. A diagnosis of relapsed MCL was made.

Over three weeks, progressive neurological deterioration occurred with ataxia, diplopia, symmetrical paraesthesia and weakness in the upper and lower limbs together with worsening pharyngeal dysphagia. Cranial nerve examination revealed globally reduced eye movements and a left VII lower motor neuron weakness. Fundoscopy was unremarkable. There was bilateral nystagmus and finger-nose ataxia. Power was reduced in a pyramidal distribution in the upper and lower limbs, tone was globally reduced. Reflexes and plantar responses were absent and sensation to light-touch and vibration was reduced in the limbs in a glove and stocking distribution to the level of the hips and shoulders. Cardio-respiratory examination was unremarkable and there was no clinical evidence of lymphadenopathy or hepatosplenomegaly.

Contrast-enhanced computerized tomography (CT) of the head, neck, thorax, abdomen and pelvis revealed low volume, mediastinal lymphadenopathy consistent with MCL. Magnetic-resonance imaging (MRI) with contrast of the brain and spinal cord demonstrated no focal parenchymal or leptomeningeal lesion.

Examination of cerebrospinal fluid (CSF) revealed scant lymphoid cells with a mature T-cell immunophenotype (CD5 positive; CD19, CD10, CD23 and FMC7 negative) but no malignant clonal population was detected. CSF protein was raised at 1.03g/L (0.15-0.45g/L) and glucose was normal at 3.7mM/L. Paired CSF and serum oligoclonal bands were identical. Nerve conduction and electromyographic (EMG) studies demonstrated severe, axonal, motor and sensory loss in the distal nerve segments of the limbs and active denervation and loss of motor units, consistent with a sensorimotor axonal neuropathy.

Other investigation revealed normal thyroid function, normal creatinine kinase and HbA1c levels. Anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (pANCA and cANCA), HIV and syphilis serology were all negative. Serum immunoglobulins were unremarkable with no evidence of a monoclonal band. An extensive search for an infectious etiology was unproductive and there were no constitutional signs to support infection. Serum complement C3 and C4 were within normal range. A bone marrow biopsy was not performed.

Serum antiganglioside antibodies were positive for GD1a, GD1b and GQ1b IgM (levels $>1/1000$ (normal = $<1/500$)); GM1, GM2, GD1a, GD1b, GQ1b IgG, IgM GM1 and IgM GM2 were negative.

On the basis of these results, a diagnosis of relapsed MCL with a paraneoplastic, motor-dominant polyneuropathy due to anti-ganglioside, onconeural antibodies was made.

Results

Initially, the patient required intensive supportive care in bed, including physiotherapy and nutritional support via a nasogastric feeding tube. Treatment for relapsed MCL was commenced with ibrutinib (560mg q.d. given via a nasogastric tube). In addition, one pulse of intravenous methylprednisolone (100mg q.d. for three days) and one course of intravenous immunoglobulin (0.4g per kilogram per day for five days) were given. After an initial improvement in neurological function, Epstein-Barr virus and cytomegalovirus, which were undetected by polymerase chain reaction (PCR) at presentation, reactivated and were treated successfully with rituximab (375mg/m² once weekly for four weeks by intravenous infusion) and intravenous ganciclovir.

Over several weeks, a global improvement in power was observed and the patient was discharged from hospital, walking with the aid of a stick. He achieved a partial remission with the use of single agent ibrutinib (560mg q.d.), but after 4 months, developed a rapid neurological relapse with lymphocytosis and died shortly afterwards.

Discussion

In this case, the differential diagnoses included a paraneoplastic polyneuropathy secondary to MCL; leptomeningeal infiltration of MCL; a late infectious complication of allogeneic stem-cell transplantation and, given the presence of anti-ganglioside antibodies, CANOMAD syndrome. CANOMAD syndrome is a rare, immune-mediated, demyelinating poly neuropathy [17-19]. The clinical features include a chronic or sub acute neuropathy with marked sensory ataxia and are flexia, typically with relatively preserved motor function. Oculo motor and bulbar motor palsies may also be present either as fixed or relapsing-remitting features [24,25]. Electrophysiological and nerve conduction studies demonstrate demyelinating and axonal neuropathies and immunological assays almost always detect the presence of a paraprotein together with anti-GQ1b and anti-disialosyl antibodies [26]. Inflammatory peripheral neuropathies, paraneoplastic neuropathies and chronic Miller-Fisher syndrome should be considered in the differential diagnosis as they may also feature demyelination due to an autoimmune or paraneoplastic process. Treatment responses have been reported with the use of intravenous immunoglobulin, rituximab and plasma exchange in some cases although response duration is often brief [20,27].

Although, in this case, the positive GD1a, GD1b and GQ1b IgM assay together with ataxia and ophthalmoplegia were consistent with CANOMAD syndrome, the balance of opinion was against this for several reasons. Firstly, the onset and progression were more acute than the classical, slowly progressing disorder with relapsing and remitting symptoms and a mean duration of 13 years. Secondly, a loss of motor function, not dyskinaesthesia, was the prominent clinical feature, which is not typical for CANOMAD. Finally, the lack of detectable paraprotein was also against the diagnosis.

Relapsed MCL with leptomeningeal infiltration was also a possible explanation. Central nervous system infiltration has a crude incidence of approximately 1% at diagnosis and 4 to 20% overall in MCL [28-32]. Weakness, confusion, ocular disturbance and headache are the most common presenting features and CSF cytology or flow cytometry are often but not always positive, even when specific radiographic lesions are present [29,30]. Leptomeningeal disease (positive cytology with normal neuro-radiological imaging) is more

frequent than parenchymal disease in MCL [28]. Although CNS MCL was suspected in this case, it was not possible to prove this from CSF analysis or neuro-radiological imaging.

A late complication of allogeneic transplantation such as infection were considered unlikely in the absence of a detectable infectious agent; a lack of constitutional upset and the patient's subsequent improvement with immunosuppression.

The most likely diagnosis was therefore a paraneoplastic, motor-dominant polyneuropathy due to anti-ganglioside, onconeural antibodies associated with relapsed MCL. Previously described treatments for PNS, including plasma-exchange and immunosuppression, have historically yielded only short-lived responses [13,33]. Furthermore, chemo-immunotherapy to treat the underlying malignancy is often difficult or inappropriate to deliver in this context because of co-existing morbidity or typically poor performance status [28].

In this case, although multiple immunomodulatory therapies, including rituximab, were initiated, an objective improvement was first observed on initiation of ibrutinib and before rituximab therapy.

Ibrutinib is an orally active, irreversible inhibitor of Bruton's tyrosine kinase, an intracellular protein downstream of the B cell receptor (BCR) responsible for regulation of cell-signalling, proliferation, migration and homing [34]. It has been shown to have potent activity against a number of B-cell malignancies, particularly chronic lymphocytic leukaemia, Waldenström's macroglobulinemia and MCL [35]. Ibrutinib is very effective and well tolerated in relapsed/refractory MCL with an overall response rate of 68% as a single agent [36]. It has also been proven to penetrate the CNS at clinically effective levels using a standard therapeutic oral dose and recent studies have yielded encouraging results in the treatment of MCL with CNS relapse [37,38]. The safety and efficacy of ibrutinib has not been previously evaluated in this context, although the suppression of onconeural antibody secretion by neoplastic B-lymphocytes is a plausible mechanism of action.

As this case demonstrates, ibrutinib is well tolerated, even in patients with significant co morbidities and can be administered via a feeding tube. It was therefore a rational choice of therapy in this case and led to remission duration comparable with more intensive therapies sometimes used in MCL with CNS involvement [30].

Conclusion

Paraneoplastic neurological disease is a rare complication of MCL and can be associated with anti-ganglioside antibodies as described in this case. Ibrutinib, in association with immunosuppressive therapy for paraneoplastic complications, is a safe and effective therapeutic option in the context of relapsed MCL with significant co-existing morbidities.

Disclosure

DT, PM, and HH have no conflicts of interest to declare. Simon Rule has received honoraria from Janssen-Cilag Ltd. and Pharmacyclics Inc. and research funding from Janssen-Cilag Ltd.

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