Successful treatment of IgM paraproteinaemic neuropathy with fludarabine

Heather C Wilson, Michael P T Lunn, Stephen Schey, R A C Hughes

Abstract

Objectives—To evaluate the response of four patients with IgM paraproteinaemic neuropathy to a novel therapy—pulsed intravenous fludarabine.

Background—The peripheral neuropathy associated with IgM paraproteinaemia usually runs a chronic, slowly progressive course which may eventually cause severe disability. Treatment with conventional immunosuppressive regimens has been unsatisfactory. Fludarabine is a novel purine analogue which has recently been shown to be effective in low grade lymphoid malignancies.

Methods—Four patients were treated with IgM paraproteinaemic neuropathy with intravenous pulses of fludarabine. Two of the four patients had antibodies to MAG and characteristic widely spaced myelin on nerve biopsy and a third had characteristic widely spaced myelin only. The fourth had an endoneurial lymphocytic infiltrate on nerve biopsy and a diagnosis of Waldenström’s macroglobulinaemia.

Results—In all cases subjective and objective clinical improvement occurred associated with a significant fall in the IgM paraprotein concentration in three cases. Neurophysiological parameters improved in the three patients examined. The treatment was well tolerated. All patients developed mild, reversible lymphopenia and 50% mild generalised myelosuppression, but there were no febrile episodes.

Conclusion—Fludarabine should be considered as a possible treatment for patients with IgM MGUS paraproteinaemic neuropathy.

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Keywords: peripheral nervous system diseases; fludarabine; paraproteins

A benign paraprotein, often called a monoclonal gammopathy of undetermined significance (MGUS), is found in about 10% of patients with idiopathic peripheral neuropathy compared with 1–3% of an age matched control population. All classes of immunoglobulin are represented but IgM accounts for 60% of cases, commonly with κ light chains. The neuropathies associated with these paraproteins are usually heterogeneous but some subgroups present with specific neuropathy syndromes. The commonest subgroup is a syndrome of IgM paraproteinaemic demyelinating neuropathy in which IgM antibodies are directed against myelin associated glycoprotein (MAG). In other patients antibodies to other peripheral nerve antigens are present such as ganglioside GM1, chondrotin sulphate, and sulphatide. The range of neuropathies differs with the different antibodies. High concentrations of anti-GM1 IgM are associated with a pure lower motor neuron syndrome with multifocal motor conduction block. IgM reactive to chondrotin sulphate or sulphatide is found in association with a predominantly sensory neuropathy. The neuropathy associated with IgM paraproteinaemia usually runs a slowly progressive course but may eventually produce appreciably disabling motor and sensory symptoms.

Evidence suggesting an aetiological role for the paraprotein is compelling, particularly in those 50%–70% of cases associated with antibodies directed against MAG. This underlies the rationale for current treatment strategies, which include conventional immunosuppressive regimes such as steroids, alkylating agents, intravenous immunoglobulin, and plasma exchange. These have produced inconsistent results and a more effective therapy to prevent chronic disability is still being sought. Fludarabine is a novel, fluorinated purine analogue which was recently shown to be effective in various low grade lymphoproliferative conditions, including IgM secreting plasma cell dyscrasias. We treated our first patient with disabling peripheral neuropathy associated with an IgM paraprotein with fludarabine with favourable results. Consequently we treated our next three consecutive patients. The results have been sufficiently encouraging to deserve reporting.

Case reports

PATIENT 1

A 45 year old woman gave a 4 year history of gradually worsening pins and needles and numbness in her fingertips and feet, occasional stabbing pains in her feet, and a tendency to trip when walking. She had required a stick and ankle splints to walk over the past year. There was no relevant medical, family, or drug history. She had been taking a moderate dose of prednisolone since a year after the onset of her symptoms with no clear benefit. Plasma exchange and intravenous immunoglobulin had also been tried without benefit.

General examination showed a cushingoid facies. There were no abnormalities in the cranial nerves. She walked unaided with difficulty with a steppage gait and bilateral footdrop, preferring to use ankle splints and a stick. Her quadriceps and distal leg muscles were wasted bilaterally. Tone was normal. Power in the arms...
was normal but there was mild finger-nose ataxia. Hip flexion was moderately weak bilaterally, knee flexion mildly, and ankle dorsiflexion markedly weak. Tendon reflexes were absent. Plantar responses were flexor. There was a stocking loss of light touch to the mid-shin and of pinprick sensation to the ankles. Joint position sense was absent at the toes and vibration sense was diminished to the knees.

Haematology, erythrocyte sedimentation rate, autoimmune profile, and biochemistry were normal. Protein electrophoresis disclosed an IgM λ paraprotein with no immunoparesis (normal concentrations of other immunoglobulins). This was quantified by densitometry at 7 g/l. Complement fixing antibodies to human sciatic nerve homogenate, assayed as described by Hughes and Stedronska, were present. Neurophysiology confirmed a severe demyelinating neuropathy. Sural nerve biopsy showed a marked reduction in myelinated fibres; surviving fibres were often demyelinated and had widely spaced myelin or formed tomacula with redundant myelin loops. Bone marrow examination gave normal results.

She was given intravenous fludarabine (25 mg/m²) daily for 5 days, repeated every 4 weeks for a total of six courses. There was a steady, ultimately dramatic, improvement in the neuropathy, beginning after the third course and sustained such that power in all muscle groups normalised except for mild weakness of intrinsic hand muscles and of ankle dorsiflexion. She became fully mobile, without the need for ankle splints or a stick. Her sensory symptoms also improved, leaving only residual numbness in her feet and lower shins and occasional pins and needles in cold weather. Furthermore, her steroids were gradually reduced, then stopped with no ill effects and the improvement was sustained 28 months after completion of fludarabine. Her paraprotein fell from 7 g/l to 2 g/l.

PATIENT 2
An 80 year old woman gave a 4 year history of burning dysaesthesia and a feeling of coldness in both feet. For 3 years she had found it increasingly difficult to walk, and had required a stick for 2 years. Over the past 2 years she had developed similar sensory symptoms in her fingertips, shooting pains in her feet and calves, and difficulty with fine finger movements. There was no other medical history. She had received a 3 month course of oral prednisolone, courses of intravenous immunoglobulin, and plasma exchange without benefit.

On examination there was mild distal limb wasting, mild bilateral weakness of shoulder abduction, finger abduction, hip flexion, and knee extension and moderate weakness of ankle dorsiflexion and extensor hallucis longus. Ankle reflexes were absent and plantar responses flexor. Light touch and pinprick sensation were diminished in the fingers and up to the mid-shin, and vibration sense and proprioception were reduced distally in the legs.

Nerve conduction tests showed a severe demyelinating peripheral neuropathy. Blood count, erythrocyte sedimentation rate, and biochemistry were normal. Autoimmune profile, extractable nuclear antibodies, ANCA, and anti-human sciatic nerve antibodies were negative. There was a mid-γ IgM λ paraprotein of 2 g/l on protein electrophoresis, with no immunoparesis. Protein concentration in CSF was mildly increased at 0.415 g/l. Skeletal survey and bone marrow biopsies were normal. Full thickness sural nerve biopsy showed a severe chronic neuropathy with ongoing degeneration and some tomaculous fibres. No demyelination or inflammation was seen but widely spaced myelin was present.

She was given intravenous fludarabine (25 mg/m²) daily for 5 days every month for 6 months. After the third course there was subjective improvement in her dysaesthesia and a modest improvement in the MRC sum score and time taken to walk 10 m, sustained at 14 months from the completion of fludarabine. The paraprotein concentration remained at 2 g/l.

PATIENT 3
A 72 year old man gave a 40 year history of intermittent tingling and numbness of his feet and hands which had progressed over the past 5 years, producing a constant numbness of the fingers, impaired manual dexterity, and increasing difficulty walking. His medical history included diphtheria as a child, hypertension, and mild congestive cardiac failure. His only medication was frusemide. There was no relevant family history.

On examination there was mild ankle oedema and moderate splenomegaly, but no other abnormality. He walked with a high stepping gait and bilateral footdrop. He was unable to walk on his heels or toes and Romberg’s test was positive. Cranial nerve examination was normal. There was bilateral distal muscle wasting and weakness more prominent in the lower than the upper limbs. All deep tendon reflexes were absent and plantar responses flexor. There was a fine postural tremor of his outstretched hands with finger-nose and heel-shin ataxia. Light touch sensation was reduced distally to the knees, pain, and temperature sensation were reduced to the mid-shin and there was loss of proprioception at the toes and of vibration sense to the anterior superior iliac crests.

Investigations showed a mild anaemia and lymphopenia. Erythrocyte sedimentation rate and biochemistry were normal. There was a mid-γ IgM λ paraprotein of 14 g/l with no immunoparesis. Skeletal survey showed degenerative cervical spine changes only. Abdominal ultrasonography showed an enlarged spleen but was otherwise normal. Bone marrow examination was normal. Analysis of CSF disclosed an increased white cell count of 190/µl with eight red cells, a protein concentration of 0.60 g/l, and a normal glucose. The CSF cytology showed an excess of lymphocytes but no lymphoblasts or other malignant cells. Oligoclonal bands were present in both CSF and serum. Neurophysiology confirmed a severe demyelinating polyneuropathy with additional bilateral carpal tunnel compression. On full thickness sural nerve biopsy there was evidence
of severe axonal loss, demyelination and remyelination, and a dense epineurial infiltrate of lymphocytes, mostly B-cells displaying both κ and λ light chain specificities. A diagnosis of Waldenström’s macroglobulinaemia with an associated neuropathy was made.

He received intravenous fludarabine (25 mg/m²) daily for 5 days every 6 weeks for a total of five courses, which he tolerated well. After the second course there was both subjective and objective improvement in sensation in his feet and left hand, and in distal strength. His spleen became impalpable and the paraprotein concentration fell to 7 g/l. Improvement continued and is maintained 14 months after completion of fludarabine.

**PATIENT 4**

This 53 year old man had developed patches of pins and needles in both feet 4.5 years earlier which had gradually progressed to a numbness of both hands and lower legs. He complained of an aching sensation in the hands and forearms and weakness of his grip. He had found it increasingly difficult to walk long distances, becoming tired after a short walk, and felt unsteady on his feet. He also complained of excessive malaise and frequent headaches. Medical history included a left carpal tunnel decompression in his 30s and persistent malaise and dysequilibrium after a viral illness 8 years earlier. There was no relevant family history and he was taking no regular medication.

General examination was normal. He walked normally unaided but was unsteady on heel-toe testing and had difficulty hopping and rising from squatting. Cranial nerve examination was normal. There was mild bilateral weakness of the dorsal interossei, hip flexion, and ankle dorsiflexion. There was generalised areflexia. Sensation to light touch was diminished distally to the wrists and mid-shins and pinprick sensation to the wrists and toes. Vibration sense and proprioception were absent at the toes. Two point discrimination was impaired to >2 cm on the index fingers. This 53 year old man had developed patches of pins and needles in both feet 4.5 years earlier which had gradually progressed to a numbness of both hands and lower legs. He complained of an aching sensation in the hands and forearms and weakness of his grip. He had found it increasingly difficult to walk long distances, becoming tired after a short walk, and felt unsteady on his feet. He also complained of excessive malaise and frequent headaches. Medical history included a left carpal tunnel decompression in his 30s and persistent malaise and dysequilibrium after a viral illness 8 years earlier. There was no relevant family history and he was taking no regular medication.

Results

Three of the four patients had received prior treatment with traditional therapies, patients 1 and 2 to an extensive degree (steroids, intravenous immunoglobulin, and plasma exchange). None had produced any notable or sustained amelioration of symptoms or signs. Patient 1 had developed cushingoid side effects from prolonged steroid therapy, which improved once fludarabine was given and steroids withdrawn.

All four patients tolerated the treatment with fludarabine well. Reported side effects comprised mild nausea, malaise, and headache. All patients developed a reversible lymphopenia and patients 2 and 4 showed evidence of mild generalised myelosuppression on routine blood tests but there were no infective or febrile episodes in any patient. Patient 2 developed chemical and clinical hepatitis that resolved after discontinuation of diclofenac, taken for an exacerbation of longstanding arthralgia.

All patients reported subjective improvement in both motor and sensory symptoms, in general beginning after the third monthly course and supported by objective gains in the MRC and sensory sum scores and a reduction in the time taken to walk 10 m (table 1). Disability was also assessed using the modified Rankin scale and improved by three points in patient 1, by one point in patient 2 and was unchanged in the other two. Patient 1 in particular showed a dramatic recovery such that she was able to walk unaided by month 4, having required bilateral ankle splints and a stick to mobilise with difficulty before treat-

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**Table 1  Summary of patient characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Duration (months)</th>
<th>Type</th>
<th>MAG (CFD)</th>
<th>GM1</th>
<th>IgM (g/l)</th>
<th>MRC sum score</th>
<th>Sensory sum score</th>
<th>10 m walk (s)</th>
<th>Modified Rankin scale</th>
<th>Nerve conduction studies</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>48</td>
<td>IgMl</td>
<td>Pos</td>
<td>Neg</td>
<td>7.0</td>
<td>2.0</td>
<td>56</td>
<td>67</td>
<td>4</td>
<td>15*</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>48</td>
<td>IgMl</td>
<td>Neg</td>
<td>Neg</td>
<td>2.0</td>
<td>2.0</td>
<td>63</td>
<td>67</td>
<td>7</td>
<td>28†</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>60</td>
<td>IgMx</td>
<td>Neg</td>
<td>Neg</td>
<td>14.0</td>
<td>7.0</td>
<td>65</td>
<td>67</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>66</td>
<td>IgMx</td>
<td>Pos</td>
<td>Neg</td>
<td>9.0</td>
<td>5.0</td>
<td>63</td>
<td>67</td>
<td>12</td>
<td>7.1</td>
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</tr>
</tbody>
</table>

*With one stick.
†With bilateral ankle splints and one stick.
‡Bilateral carpal tunnel syndromes also noted.

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*Note: MRC, Medical Research Council; SAP, sensory action potential; GM1, glycolipid GM1; CFT, complement fixation test; Pre, pre-treatment; Post, post-treatment.*
Table 2: Summary of published treatment trials of IgM paraproteinaemic neuropathy

<table>
<thead>
<tr>
<th>Author et al</th>
<th>Pt</th>
<th>IgM MGUS MAG</th>
<th>Treatment</th>
<th>Median FU (mo)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalakas and Engel 1981</td>
<td>5</td>
<td>2</td>
<td>NK</td>
<td>Prednisolone +/- chlorambucil daily</td>
<td>54</td>
</tr>
<tr>
<td>Melmed et al 1983</td>
<td>3</td>
<td>3</td>
<td>NK</td>
<td>Prednisolone / PEx / chlorambucil / azathioprine</td>
<td>NS</td>
</tr>
<tr>
<td>Sherman et al 1984</td>
<td>10</td>
<td>5</td>
<td>NK</td>
<td>PEx repeated +/- chlorambucil</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Ernerudh et al 1989</td>
<td>3</td>
<td>3</td>
<td>NK</td>
<td>PEx repeated</td>
<td>10</td>
</tr>
<tr>
<td>Smith et al 1987</td>
<td>8</td>
<td>6</td>
<td>NK</td>
<td>PEx repeated +/- chlorambucil</td>
<td>21</td>
</tr>
<tr>
<td>Kelly et al 1988</td>
<td>10</td>
<td>8</td>
<td>NK</td>
<td>PEx + prednisolone + chlorambucil / azathioprine / cyclophosphamide</td>
<td>6</td>
</tr>
<tr>
<td>Haas and Tatum 1988</td>
<td>5</td>
<td>5</td>
<td>NK</td>
<td>Chlorambucil +/- cyclophosphamide +/- prednisolone</td>
<td>14</td>
</tr>
<tr>
<td>Donefris and Kelly 1989</td>
<td>1</td>
<td>1</td>
<td>NK</td>
<td>PEx / prednisolone / azathioprine / TLI</td>
<td>NS</td>
</tr>
<tr>
<td>Cook et al 1990</td>
<td>2</td>
<td>2</td>
<td>NK</td>
<td>IVIG repeated</td>
<td>NS</td>
</tr>
<tr>
<td>Dyck et al 1991</td>
<td>39</td>
<td>21</td>
<td>NK</td>
<td>PEx / Sham repeated (double blind)†</td>
<td>≤30</td>
</tr>
<tr>
<td>Ernerudh et al 1992</td>
<td>5</td>
<td>5</td>
<td>NK</td>
<td>Prednisolone +/- chlorambucil / PEx / melphalan</td>
<td>≤12</td>
</tr>
<tr>
<td>Leger et al 1994</td>
<td>13</td>
<td>13</td>
<td>NK</td>
<td>IVIG</td>
<td>12</td>
</tr>
<tr>
<td>Siciliano et al 1994</td>
<td>3</td>
<td>1</td>
<td>NK</td>
<td>Selective apheresis</td>
<td>7/10 improved</td>
</tr>
<tr>
<td>Sherman et al 1994</td>
<td>10</td>
<td>10</td>
<td>NK</td>
<td>Cyclical fludarabine</td>
<td>17</td>
</tr>
<tr>
<td>Blume et al 1995</td>
<td>4</td>
<td>2</td>
<td>NK</td>
<td>Cyclical repeated PEx + cyclophosphamide</td>
<td>12</td>
</tr>
<tr>
<td>Oksenhendler et al 1996</td>
<td>44</td>
<td>44</td>
<td>NK</td>
<td>Chlorambucil or chlorambucil / PEx (open)†</td>
<td>14</td>
</tr>
<tr>
<td>Notermans 1996</td>
<td>16</td>
<td>10</td>
<td>5</td>
<td>Prednisolone + cyclical cyclophosphamide</td>
<td>36</td>
</tr>
<tr>
<td>Notermans et al 1997</td>
<td>15</td>
<td>12</td>
<td>6</td>
<td>PEx or IVIG or prednisolone (cyclophosphamide for relapse)</td>
<td>36</td>
</tr>
<tr>
<td>Mariette et al 1997</td>
<td>20</td>
<td>20</td>
<td>NK</td>
<td>IVIG or interferon-α (open)†</td>
<td>12</td>
</tr>
<tr>
<td>Notermans et al 1998</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>High dose pulsed intravenous dexamethasone</td>
<td>19</td>
</tr>
</tbody>
</table>

* 7/7 PEx improved, 2/6 IVIG improved, 1/2 prednisolone improved, then 3/5 primary failures improved with PEx or cyclophosphamide.
† Randomised; PEx=plasma exchange; IVIG=intravenous immunoglobulin; NS=not specified; 1=patient with IgM apparently MAG positive; cases other than IgM MGUS (for example, amyloidosis, lymphoma, or Waldenström’s macroglobulinaemia) are excluded.

Discussion

The rationale for treating IgM paraproteinaemic neuropathy is based on the assumption (derived from considerable evidence) that the IgM paraprotein is causally linked to the neuropathy. Therapies to date have aimed to reduce the paraprotein concentration by targeting the monoclonal B-cell clone or removing the antibody, or to interfere with presumed effector mechanisms such as complement activation and macrophage recruitment.

There are only limited published data regarding efficacy of the various immunosuppressive regimes in IgM paraproteinaemic neuropathies and only four randomised controlled trials (table 2). Most case series are small and include diverse groups of patients (for example, IgG paraproteins, chronic inflammatory demyelinating polyradiculoneuropathies, lymphomas, amyloid or Waldenström’s macroglobulinaemia, or other complicating conditions such as cervical spondylosis). Dyck et al compared plasma exchange to sham exchange in 39 patients, 21 of whom had an IgM paraprotein. They found a significant difference in favour of plasma exchange in the IgG and IgA subgroups (an improvement in the neuropathy disability scale (weakness)) but no significant difference in the IgM subset. Changes in disability were not reported. Improvement has been reported in nine of 11 cases of IgM paraprotein associated neuropathy in three further small studies of plasma exchange, sustained at 10, 18, and 36 months respectively. Siciliano et al reported benefit in one patient with an IgM paraprotein treated with selective apheresis. Improvement with plasma exchange in combination with either pulsed intravenous cyclophosphamide or chlorambucil has been reported in 25% to 100% of patients in small studies with follow up periods ranging from 5 to 34 months.

Less information is available regarding response to steroid therapy. Four of five patients treated with pulsed high dose intravenous dexamethasone improved but the incidence of psychiatric side effects was unacceptably high. Steroids have been used in combination with azathioprine, cyclophosphamide, chlorambucil, and plasma exchange in several small studies, with improvement in 0% to 100% of patients at 14 to 54 months of follow up.

Dalakas et al carried out a double blind, randomised, cross over, placebo controlled study of intravenous immunoglobulin in 11 patients with IgM MGUS. Two patients showed...
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G-CSF, has recently been introduced in de novo and relapsed acute myelogenous leukaemia. Cumulative myelosuppression and immunosuppression are the principal side effects. Lymphopaenia can be severe and is usually prolonged. Febrile episodes and atypical infections (such as Listeria monocytogenes sepsis and Pneumocystis pneumonia occur in 20% of patients treated, sometimes 6 to 9 months after completion of therapy. However, these are considerably more frequent in non-responders or those with extensive prior or combination therapy. Extramedullary toxicity is rare, comprising mainly nausea, stomatitis, and diarrhoea. Proprioxaxis against Pneumocystis pneumonia (cotrimoxazole or pentamidine) is given routinely throughout treatment, and until the lymphocyte count recovers to normal. Bimonthly monitoring of myelosuppression and constant vigilance for opportunistic infection are essential. Fludarabine is usually administered under the supervision of a haematologist.

Because of its activity in low grade B cell lymphoid malignancies and its favourable side effect profile when compared with traditional therapies, fludarabine is a strong candidate for the treatment of IgM paraproteinaemic neuropathy. In an abstract, Sherman et al. recently reported treating 10 patients with IgM paraproteinaemic neuropathy with fludarabine. Of these, eight had anti-MAG antibodies and two had anti-GM1 antibodies. Seven of the eight MAG positive patients improved clinically, six with a corresponding reduction in IgM titre of over 50%. The two with anti-GM1 antibodies seemed resistant. The favourable response of our four patients to fludarabine further supports its potential role in the management of IgM paraproteinaemic neuropathy.

Although only a minority of the authors have reported the IgM paraprotein concentration in response to therapy, some have found a fall coinciding with clinical improvement. We regard the >25% fall in the paraprotein concentration coincident with treatment seen in three of our four patients as meaningful and relevant.

No authors have measured disability and there are no data available on long term effects, the maximum follow up period being 54 months. These treatments are time consuming, expensive, or have a relatively high incidence of side effects and are not usually used until appreciable disability has developed.

Fludarabine is a novel, fluorinated purine analogue. It is a potent molecule with a wide range of biochemical effects and is efficacious in a wide variety of low grade lymphoid malignancies. It is the most effective agent for Waldenström’s macroglobulinaemia, a low grade lymphoid malignancy characterised by the presence of plasmacytoid lymphocytes that produce monoclonal IgM. Fludarabine achieves response rates in excess of 50% in previously untreated patients, and in the region of 40% among previously treated patients. Furthermore, 18% of refractory cases respond. These statistics compare favourably with those produced by traditional first line therapies, commonly alkylating agents, often in combination with steroids or other chemotherapeutic agents. Fludarabine is effective in previously untreated low grade lymphoma, obtaining response rates of 50% to 79% when used as a single agent, arguably showing superior activity compared with traditional therapies such as anthracyclines and alkylating agents. Fludarabine also produces complete remission in a greater proportion of patients than does conventional chemotherapy and molecular remissions have been found, a rare phenomenon with currently available chemotherapies. In chronic lymphocytic leukaemia, promising results have been produced using fludarabine alone or in combination with cyclophosphamide or mitoxantrone and dexamethasone. It also seems to show activity in de novo myelodysplastic syndrome in combination with other chemotherapies and drugs, cutaneous T cell lymphoma, and hairy cell leukaemia but multiple myeloma is resistant. Fludarabine, in combination with cytokine arabinoside (with which it shows striking synergism) and

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