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Summary. Mantle cell lymphoma is an aggressive B-cell lymphoma with a poor median survival despite conventional therapy. Here, we present the case of a patient with multiply relapsed mantle cell lymphoma, having failed treatment with chemotherapy, steroids and rituximab. He was treated with single-agent thalidomide at a dose of 800 mg daily and entered a good partial remission which was maintained for the next 6 months. There is clearly a need for further studies of thalidomide in mantle cell lymphoma to confirm this promising initial result.

Keywords: mantle cell lymphoma, thalidomide.

Mantle cell lymphoma is an aggressive B-cell lymphoma, accounting for approximately 7% of adult lymphomas in Europe and America. Response to conventional chemotherapy is poorly maintained, with a median survival of only 3 to 4 years. Recent trials of newer therapies, including fludarabine, rituximab and autologous stem cell transplantation, have likewise proved disappointing (Freedman *et al*, 1998). Here, we present the case of a multiply relapsed patient with chemotherapy resistant disease who entered a good partial remission following treatment with thalidomide alone.

CASE REPORT

A 68-year-old man presented in December 1997 with stage IVa mantle cell lymphoma. He opted to delay treatment until July 1998 when he started a 9 month course of pulsed oral chlorambucil. This achieved a moderate reduction in lymphadenopathy but progression was evident 6 months later, in August 1999, with the onset of severe diarrhoea and pancytopenia [Hb 5·0 g/dl, white blood cell (WBC) count $2{\cdot}2 \times 10^9$/l, neutrophils $1{\cdot}1 \times 10^9$/l, platelets 44×10^9/l]. Investigations revealed extensive marrow infiltration, markedly increased lymphadenopathy and splenomegaly, and a new hepatic peri-hilar infiltrate. He underwent six cycles of CHOP (cyclophosphamide, hydroxydaunomycin, oncovin, prednisone) chemotherapy, achieving a major reduction in lymphadenopathy and normalization of his blood count. This lasted only until June 2000, with the onset of jaundice from a lymph node mass encasing the bile duct. He was treated with MIDAC (mitozantrone 10 mg/m^2 and cytarabine 500 mg/m^2 for 3 d) and suffered a stormy post-chemotherapy course with prolonged neutropenic fever. He remained free of jaundice, although a computerized tomography (CT) scan the following month showed static disease. He declined further chemotherapy and, in August 2000, underwent a 4 week course of rituximab 375 mg/m^2 per week. His response, however, lasted only 4 weeks when he again deteriorated with diarrhoea, jaundice and pancytopenia (Hb 8·7 g/dl, WBC $30{\cdot}5 \times 10^9$/l, neutrophils $2{\cdot}4 \times 10^9$/l, platelets 54×10^9/l) with exfoliating lymphoma cells in his peripheral blood. He was started on prednisolone 60 mg daily and two doses of vinblastine 10 mg were administered over the following month. His jaundice again cleared but he remained severely pancytopenic (Hb 7·8 g/dl, WBC $4{\cdot}7 \times 10^9$/l, neutrophils $0{\cdot}5 \times 10^9$/l, platelets 20×10^9/l) and disease progression was evident on a CT scan in November 2000. Four days of dexamethasone 40 mg was tried with no response and, in December 2000, he was started on thalidomide 200 mg, increased to 400 mg after 2 weeks. A few days later, he was readmitted severely unwell with jaundice, pyrexia and melaena. He remained profoundly pancytopenic (Hb 7·1 g/dl, WBC $1{\cdot}8 \times 10^9$/l, neutrophils $0{\cdot}3 \times 10^9$/l, platelets 8×10^9/l) and it was suspected that he was bleeding from lymphomatous involvement of his bowel. Endoscopy showed a moderate haemorragic gastritis, and he was managed supportively with blood products and antibiotics. His pyrexia and melaena settled over the next 2 weeks but his general condition remained very poor. The thalidomide was increased to 800 mg daily and he was transferred to a

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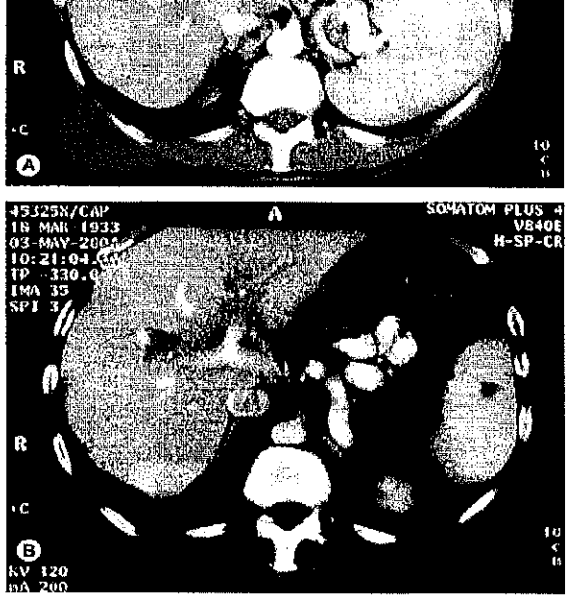

Fig 1. Abdominal CT scan (A) in July 2000, showing splenomegaly and extensive lymphomatous infiltration at the porta-hepatis, and (B) in May 2001, showing over 50% reduction in disease bulk.

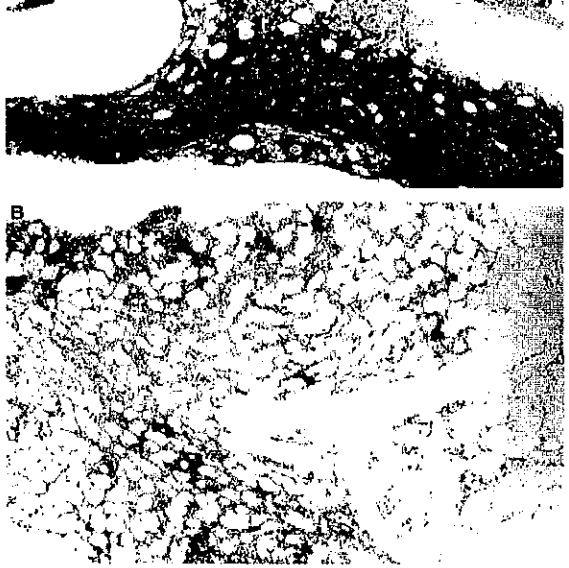

Fig 2. Bone marrow trephine stained for CD20 (A) in August 2000, showing extensive paratrabecular infiltration by lymphoma, and (B) in May 2001, showing a hypocellular marrow but with significantly less lymphocytic infiltrate.

hospice for terminal care. His clinical condition, however, progressively improved over the next 2 months and he was discharged home in February 2001. His liver function tests normalized and there was a dramatic improvement in his peripheral blood count (Hb 12·8 g/dl, WBC $3{\cdot}4 \times 10^9$/l, neutrophils $2{\cdot}1 \times 10^9$/l, platelets 119×10^9/l). Over the next 4 months, he remained in a good general condition apart from the development of a spontaneous deep vein thrombosis and leg ulcers. Disease reassessment showed over 50% reduction in lymphadenopathy on a CT scan (Fig 1) and a generally hypocellular bone marrow trephine with a marked reduction in the lymphoid infiltrate (Fig 2). In July 2001, he again became pancytopenic (Hb 9·0 g/dl, WBC $0{\cdot}8 \times 10^9$/l, neutrophils $0{\cdot}25 \times 10^9$/l, platelets 95×10^9/l) and rapidly succumbed to a fatal septicaemia from a urinary tract infection. Unfortunately, owing to the speed of his final deterioration, it was not possible to further investigate the cause of his pancytopenia or the state of his disease at that time.

DISCUSSION

This case demonstrates many typical features of mantle cell lymphoma. The majority of patients are male and present in the seventh decade of life with stage IV disease. After 3 years of treatment, his lymphoma was resistant to both chemotherapy and steroids and had progressed following treatment with rituximab. He had developed bone marrow failure, severe gastro-intestinal bleeding and jaundice, and was entering the terminal phase of his illness. Two months following the introduction of thalidomide, he demonstrated a dramatic response that was sustained for a further 6 months.

After many years in disrepute for its teratogenicity and neurotoxicity, there has been a recent revival of interest in thalidomide for its antitumour effects. This has been most extensively studied in myeloma where a 30% response rate has been documented in refractory and relapsed disease (Singhal *et al*, 1999; Alexanian & Weber, 2000; Munshi *et al*, 2000). Ongoing studies are investigating its effectiveness in early myeloma as well as in other haematological and solid malignancies (Alexanian *et al*, 2000). It has been used with some success in low-grade lymphoplasmacytoid lymphoma (Dimopoulos *et al*, 2001), however, its use in mantle cell lymphoma has not previously been reported.

Thalidomide was initially used in myeloma for its activity against angiogenesis, which has recently been implicated in the development of haematological malignancies. Neovascularization of the bone marrow occurs in both myeloma

2000), which is elevated in some lymphoma patients and associated with a poorer prognosis (Salles *et al*, 1996). Despite our knowledge of these diverse biological actions, the precise mechanism of thalidomide's antitumour effect remains undetermined.

Thalidomide is not a cytotoxic agent and may, therefore, be well tolerated by patients with bone marrow failure. Neutropenia has occurred in up to 25% of human immunodeficiency virus (HIV) patients on thalidomide but this has rarely occurred in myeloma patients (Clark *et al*, 2001). Of concern is the possible association between thalidomide and venous thromboembolism. This has been observed in patients receiving combined thalidomide and chemotherapy but not in those receiving thalidomide alone (Zangari *et al*, 2001). Results of other studies are needed to confirm this association and to more accurately quantify the risk. Other known adverse effects include sedation, rash, peripheral oedema, dyspnoea, hypotension, peripheral neuropathy and constipation (Clark *et al*, 2001).

This case demonstrates the effect of thalidomide against multiply relapsed mantle cell lymphoma, following treatment with chemotherapy, steroids and rituximab. The result is similar to that obtained in myeloma, with less than 2 months to onset of action and a median remission of 7 months (Alexanian & Weber, 2000; Munshi *et al*, 2000). There is clearly a need for further studies of thalidomide in mantle cell lymphoma.

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