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## CASE REPORT

## Long-term stabilisation of myeloma with curcumin

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## SUMMARY

Myeloma is a haematological malignancy which typically follows a relapsing-remitting course. While treatment can control the myeloma and improve quality of life for given periods of time, remissions generally become progressively shorter with subsequent relapses, and patients ultimately enter a final refractory phase. To help control symptoms and enhance quality of life, some patients use complementary therapies as an adjunct to their conventional therapy. Here, we describe a myeloma patient who started a daily dietary supplement of curcumin when approaching her third relapse. In the absence of further antimyeloma treatment, the patient plateaued and has remained stable for the last 5 years with good quality of life.

## BACKGROUND

Myeloma is a B-cell malignancy that is characterised by the monoclonal expansion and accumulation of abnormal plasma cells within the bone marrow. Clinical manifestations include bone pain, renal impairment, recurrent infections and anaemia.<sup>1</sup> Over the past decade, advances in the understanding of the disease, together with the development of several novel treatments, have led to significant improvements in overall survival.<sup>2</sup>

Despite this, myeloma remains incurable, with a median overall survival of 5.2 years from diagnosis.<sup>3</sup> The course of the disease is typically one of recurrent remission and relapse. However, patients progressively acquire resistance to treatment and subsequent remissions become shorter and shorter. Eventually, either they run out of treatment options or become refractory to them.

In an effort to improve long-term outcomes, some myeloma patients seek to use dietary supplements, mostly for palliative purposes. While they may help to improve quality of life, there is little evidence they can increase survival.<sup>4</sup> Among them, curcumin, the active constituent of turmeric, has gained popularity as a complementary therapy in several cancers.

Here, we present a case of a heavily pretreated relapsing myeloma patient who, in the absence of further treatment options at the time, started daily curcumin and has since remained stable for the past 5 years.

## CASE PRESENTATION

A woman aged 57 years was initially diagnosed with monoclonal gammopathy of undetermined significance (MGUS) in 2007 following an incidental finding of M-protein (18 g/L) during investigation for hypertension.

Within 15 months, the patient had rapidly progressed to ISS stage 3 myeloma with M-protein 49 g/L, urinary protein 1.3 g/24-hour, Bence-Jones protein 1.0 g/24-hour, Hb 9.7 g/dL and increasing back pain. She initially declined antimyeloma treatment but 6 months later, following vertebral collapse at T5 and T12, started cyclophosphamide, thalidomide and dexamethasone (CTD) treatment. However, after a week, the patient was admitted with idiosyncratic syndrome including hyponatraemia, a fall in albumin and worsening of blood counts. She received red cell transfusion and her electrolyte abnormalities were carefully corrected.

Although there was evidence of a response to CTD (M-protein 34 g/L), bortezomib and dexamethasone treatment was initiated as an alternative, but this was discontinued after three cycles due to progressive disease (M-protein 49 g/L). The patient was then treated with lenalidomide and dexamethasone with the aim of reducing disease burden prior to high-dose therapy and autologous stem cell transplantation. Treatment was frequently interrupted and dose adjusted to account for neutropenia and despite a minor response after six cycles (starting M-protein 47 g/L, finishing M-protein 34 g/L), in October 2009, she proceeded with stem cell mobilisation. However, neither cyclophosphamide nor plerixafor/GCSF priming were successful. A bone marrow biopsy revealed 50% myeloma cells and a course of CTD was restarted with cautious titration of thalidomide.

The patient achieved a partial response with CTD retreatment over the course of 17 cycles (M-protein 13 g/L) with no further episodes of idiosyncratic syndrome. However, attempts to harvest stem cells in February 2011 and again three months later, both failed. By then, her M-protein had risen to 24 g/L and the patient was too neutropenic to be considered for a clinical trial.

At this point, the patient began a daily regime of oral curcumin complexed with bioperine (to aid absorption), as a single dose of 8 g each evening on an empty stomach. A few months later, she also embarked on a once-weekly course of hyperbaric oxygen therapy (90 min at 2 ATA) which she has maintained ever since. Her paraprotein levels gradually declined to a nadir of 13 g/L, her blood counts steadily improved and there was no evidence of further progressive lytic bone disease.

## OUTCOME AND FOLLOW-UP

The patient continues to take oral curcumin 8 g daily without further antimyeloma treatment. Over the last 60 months, her myeloma has remained stable with minimal fluctuation in paraprotein level, her blood counts lie within the normal range and



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she has maintained good quality of life throughout this period. Repeat bone imaging in 2014 identified multiple lucencies <1 cm in the right hip and degenerative changes in both hips, but these were attributed to osteoarthritis rather than the myeloma. Recent cytogenetic analysis revealed she had no abnormal cytogenetics by fluorescent in situ hybridisation.

## DISCUSSION

A small but significant number of myeloma patients consume dietary supplements in conjunction with conventional treatment primarily to help cope with the side effects of treatment, manage symptoms and enhance general well-being. Few, if any, use dietary supplementation as an alternative to standard anti-myeloma therapy. Here, we describe a case in which curcumin has maintained long-term disease control in a multiply-relapsed myeloma patient. To the best of our knowledge, this is the first report in which curcumin has demonstrated an objective response in progressive disease in the absence of conventional treatment.

Curcumin is a polyphenol derived from the perennial herb *Curcuma longa* (turmeric) and has, for centuries, been used as a traditional Indian medicine. Several reports published over the two decades have claimed various health benefits of curcumin and this has led to its increasing popularity as a dietary supplement to prevent or treat a number of different diseases.<sup>5 6</sup>

The biological activity of curcumin is indeed remarkable. It is a highly pleiotropic molecule which possesses natural antioxidant, anti-inflammatory, antiseptic and analgesic properties.<sup>7</sup> More recently, it has demonstrated antiproliferative effects in a wide variety of tumour cells including myeloma cells and exerts its antiproliferative effects through multiple cellular targets that regulate cell growth and survival.

In vitro, curcumin prevents myeloma cell proliferation through inhibition of IL-6-induced STAT-3 phosphorylation and through modulation of the expression of NF- $\kappa$ B-associated proteins such as I $\kappa$ B $\beta$ , Bcl-2, Bcl-xL, cyclin D1 and IL-6<sup>8</sup> and apoptosis-related molecules including p53 and Bax.<sup>9</sup> In other studies, curcumin was shown to circumvent resistance to dexamethasone, doxorubicin and melphalan as well as potentiate the effects of bortezomib, thalidomide<sup>10</sup> and lenalidomide.<sup>11</sup> Furthermore, curcumin-induced cell death was not influenced by myeloma molecular heterogeneity.<sup>12</sup>

The antimyeloma effects of curcumin in the clinical setting however are less clear. Only one phase I/II study has evaluated curcumin treatment in myeloma patients. These patients were either asymptomatic, relapsed or had plateau phase disease. Treatment with curcumin downregulated the expression of NF $\kappa$ B, COX-2 and STAT3 in peripheral blood mononuclear cells, but no objective responses were observed in any subgroup of patients.<sup>13</sup> This may be as a result of small sample size in this study, follow-up was limited to 3 months and clinical responses may have been observed with longer follow-up. However, downregulation of NF $\kappa$ B, COX-2 and STAT3 expression may not correlate with the clinical activity of curcumin and there may be further mechanisms of action that remain unclear, possibly through the modulation of another target. We would not be able to identify any patient-specific mechanisms of activity in this case study, as the patient has been taking curcumin for some time now and baseline bone marrow or peripheral blood samples are not available. However, in the setting of a clinical trial, it may be possible to use next-generation sequencing to help identify a mutation that may be a potential target for curcumin.

Another study examined its effects in preventing the progression of MGUS and smouldering myeloma to myeloma.<sup>14 15</sup> The results showed that curcumin exerted a trace of biological activity with modest decreases in free light chain and paraprotein levels and a reduction in a marker of bone resorption with curcumin treatment, suggesting the therapeutic potential of curcumin in MGUS and smouldering myeloma. However, more studies are needed to address this further.

Whether such effects are observed in patients with active disease remains to be seen. The fact that our patient, who had advanced stage disease and was effectively salvaged while exclusively on curcumin, suggests a potential antimyeloma effect of curcumin. She continues to take daily curcumin and remains in a very satisfactory condition with good quality of life. This case provides further evidence of the potential benefit for curcumin in myeloma. We would recommend further evaluation of curcumin in myeloma patients in the context of a clinical trial.

## Learning points

- ▶ Myeloma is a relapsing-remitting cancer for which there is currently no cure.
- ▶ Curcumin, a polyphenol derived from turmeric, has been used for many years in some herbal remedies.
- ▶ We report a case of a myeloma patient with advanced myeloma who, in the absence of conventional treatment, plateaued and has remained stable for many years with daily curcumin.
- ▶ Dietary supplements, such as curcumin, may be beneficial for some myeloma patients.

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**Contributors** AZ and JC involved in treating the described patient initially discussed and planned writing this case. The planning was made with ML of Myeloma UK. Each performed a review of the literature and a summary of the case was provided by AZ and JC to ML who wrote the initial draft. The final paper was edited by AZ and reviewed and edited by JC.

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