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Letter to Editor

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Long-term follow-up of curcumin treated MGUS/SMM patients – an updated single centre experience

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Multiple myeloma (MM) evolves through a spectrum of disease from a premalignant stage of monoclonal gammopathy of undetermined significance (MGUS) (serum M-protein value of <30 g/L, bone marrow plasma cells <10%, no or small amount of M-protein in the urine, and absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency) to an intermediate stage of smoldering multiple myeloma (SMM) (serum M protein level >30 g/L and/or bone marrow plasma cells >10%, plus no anaemia, hypercalcemia, renal failure, or lytic bone lesions) and finally presents with symptoms and signs of end-organ damage which leads to the diagnosis of MM [1]. Studies indicate that almost all cases of MM are preceded by the precursor state of MGUS or SMM [2].

Patients with MGUS or SMM are not offered therapeutic options to date and standard of care remains observation with re-evaluations of the patient every 3-4 months. Long-term monitoring of untreated MGUS/SMM patients has shown that the monoclonal protein can disappear spontaneously during follow-up only in MGUS patients with low initial concentrations of monoclonal protein (5 g/L) [3]. There are no reports of the monoclonal protein decreasing or disappearing spontaneously in SMM patients.

Because symptomatic myeloma may not evolve for as long as 20 years, it is currently not possible to predict the clinical course of MGUS or SMM. Features predicting patients at highest risk of disease progression include the size and type of M-protein, with IgA having a higher risk compared to IgG paraprotein, % plasma cell dyscrasia, and abnormal serum-free light chain ratio. A number of studies have shown that independent of the size and type of the serum M-protein, an abnormal free lightchain (FLC) ratio increases the risk of progression [4].

Given the uncertainty of disease progression with MGUS and SMM, early intervention aimed at potentially slowing down or stopping disease progression might be therapeutic. Curcuma longa (turmeric) is a tropical plant native to southern and southeastern tropical Asia. It is a perennial herb belonging to the ginger family. The most active component in turmeric is curcumin [5]. Curcumin has been shown to inhibit the proliferation of multiple myeloma cells through the downregulation of IL-6 and NF-kB. Bharti et al. showed that curcumin suppresses proliferation and induces apoptosis in multiple myeloma cells through the suppression of RANKL signaling [6].

Based on its antimyeloma cell activity, we have performed a number of studies with curcumin in MGUS/SMM patients, including a randomised, double-blind placebo- controlled cross-over study, published in the American Journal of Hematology [7] where we showed that treatment of MGUS/SMM patients with curcumin resulted in an improvement in markers of disease progression (*i.e.,* free light-chain ratio (rFLC), paraprotein levels, percentage plasma cells) in some patients [8]. A number of patients who participated in our studies and who showed a benefit, have continued to take curcumin over a number of years, of their own volition, even though the studies in which they were participating are complete.

We present here an update on the long-term follow-up of 13 MGUS/SMM patients who have been taking curcumin (at a dose of 4 -8 grams daily) for a period of 3-9 years (Table 1). The patients are monitored every 3-6 months with blood tests being done at each monitoring visit. As far as we know, we are the only centre treating MGUS/SMM patients with curcumin.

From the table, it can be seen that there are 6 MGUS and 7 SMM patients, 11 are IgG, 1x IgA and 1x IgM. Eight have kappa disease and 5 have lambda disease. Six patients are male and 7 females and the average age is 68 years. The median time of curcumin administration is 5.6 years and only one patient has developed progressive disease (patient no. 8 - cardiac amyloidosis) after 6 years of curcumin therapy. This patient has commenced anti-myeloma therapy. Five patients showed a decrease in paraprotein levels, 3 increased slightly while the rest remained stable. The bone marrow plasma cells decreased in 4 patients and increased modestly in 2 others while it remained the same in 3. Three MGUS patients have not had bone marrow aspirates/biopsies done. Five patients showed a decrease in hemoglobin while it increased slightly or remained stable in the others. Whilst the involved free light chain increased in most patients, this was accompanied by an increase in the uninvolved free light chain in most of the patients, leading to a decrease in ratio in 3 of the patients.

There is currently much debate about early treatment of high risk SMM patients, with updated IMWG diagnostic criteria for early treatment. These include serum free-light chains ratio >100, >60% plasma cells and >1 focal lesion by MRI. Several trials have been initiated to test early intervention in high-risk SMM patients. While some of the trials have shown benefit to high risk SMM patients, most of these trials have been associated with toxic events which has included hematologic events (neutropenia, thrombocytopenia, anemia) and nonhematologic events (infection, rash, asthenia, constipation, diarrhoea, deep-vein thrombosis).

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Table 1. MGUS/SMM patient responses after years of curcumin therapy.Pt no: patient number; M: male; F: female; curc yrs: curcumin years; Hb: haemoglobin; Pp: paraprotein; Bsl: baseline (at start of curcumin therapy); Eos: end of study period; iflc: involved free light chain; uiflc: uninvolved free light chain; rflc: free light chain ratio; % pc: percentage plasma cells; tp: total protein.

Pt no.	sex	age	Pp	Curc yrs	Bsl Hb (119-160g/L)	Eos Hb (119-160g/L)	Bsl pp (g/L)	Eos pp (g/L)	Bsl iflc (mg/L)	Eos iflc (mg/L)	Bsl uiflc (mg/L)	Eos uiflc (mg/L)	Bsl rflc (0.3-1.7)	Eos rflc (0.3-1.7)	Bsl % pc	Eos % pc	Bsl tp (64-83g/L)	Eos tp (64-83g/L)
1	M	71	IgGk	9	133	136	26	13.6	225	226	9.59	12.4	23.46	18.2	5	5	91	85
2	M	55	IgGk	7	109	111	28.5	16.1	97.7	1090	3.65	236	26.77	4.6	33	29	91	73
3	M	73	IgGk	5	128	134	32	37	29	31	19	11	1.53	2.82	44	25	91	94
4	M	74	IgGL	9	136	110	27	24.7	53.2	98.8	15.7	50.7	0.3	0.5	7	18	87	86
5	M	74	IgGL	3	141	111	28	28	64	83	6	10	0.09	0.12	20	11	95	86
6	F	89	IgAk	3	135	106	11.6	12	417	551	10.9	5.3	38.3	104	15	15	71	65
7	M	50	IgGL	6	144	139	29	34.6	15	41.3	6.8	8.95	0.45	0.2	10	10	101	101
8	F	77	IgGk	6	117	102	24.5	20.8	132	455	6.02	8.3	21.93	54.8	6	19	91	81
9	F	63	IgGk	5	122	128	25	19.8	54.1	114	5.82	7.2	9.3	15.8	16	15	86	83
10	F	51	IgGk	3	132	132	10	10	29	33	20	17	1.88	1.94			74	73
11	F	64	IgGL	3	134	130	11.5	11.4	10.2	9.1	1.9	6.3	0.2	0.7			80	72
12	F	66	IgMk	3	138	141	12	15.3	577	704	2	2.8	288.5	251.4			73	78
13	F	73	IgGL	3	131	112	17	17	61	93	4	7	0.07	0.08	7	8	79	76

Our data suggest that curcumin administration may benefit some patients diagnosed with MGUS or SMM with little or no toxicity even after 9 years of therapy. Future studies should assess the role of curcumin in both MGUS and SMM patients – prior to progression to high risk or active myeloma – as this may lead to a delay in or may even stop disease progression. Although one patient has progressed to amyloidosis, the other twelve have maintained stable disease with no clear evidence of disease progression. Patient tolerance has been good and none have developed clinical infections. The drawback of this correspondence is the small number of patients on long-term curcumin therapy.

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There is no conflict of interest to declare.

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