2016

Addition of rice bran arabinoxylan to curcumin therapy may be of benefit to patients with early-stage B-cell lymphoid malignancies (monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or stage 0/1 chronic lymphocytic leukemia): a preliminary clinical study

Terry Golombick
St. George Hospital, terry.golombick@sesiahs.health.nsw.gov.au

Terrence H. Diamond
St. George Hospital, terrydiamond@optusnet.com.au

Arumugam Manoharan
University of Wollongong, arumugam@uow.edu.au

Raj Ramakrishna
University of Wollongong, raj@uow.edu.au

Publication Details

Golombick, T., Diamond, T. H., Manoharan, A. & Ramakrishna, R. (2016). Addition of rice bran arabinoxylan to curcumin therapy may be of benefit to patients with early-stage B-cell lymphoid malignancies (monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or stage 0/1 chronic lymphocytic leukemia): a preliminary clinical study. Integrative Cancer Therapies, 15 (2), 183-189.

Addition of rice bran arabinoxylan to curcumin therapy may be of benefit to patients with early-stage B-cell lymphoid malignancies (monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or stage 0/1 chronic lymphocytic leukemia): a preliminary clinical study

Abstract

Hypothesis. Prior studies on patients with early B-cell lymphoid malignancies suggest that early intervention with curcumin may lead to delay in progressive disease and prolonged survival. These patients are characterized by increased susceptibility to infections. Rice bran arabinoxylan (Ribraxx) has been shown to have immunostimulatory, anti-inflammatory, and proapoptotic effects. We postulated that addition of Ribraxx to curcumin therapy may be of benefit.

Study design. Monoclonal gammopathy of undetermined significance (MGUS)/smoldering multiple myeloma (SMM) or stage 0/1 chronic lymphocytic leukemia (CLL) patients who had been on oral curcumin therapy for a period of 6 months or more were administered both curcumin (as Curcuforte) and Ribraxx.

Methods. Ten MGUS/SMM patients and 10 patients with stage 0/1 CLL were administered 6 g of curcumin and 2 g Ribraxx daily. Blood samples were collected at baseline and at 2-month intervals for a period of 6 months, and various markers were monitored. MGUS/SMM patients included full blood count (FBC); paraprotein; free light chains/ratio; C-reactive protein (CRP)and erythrocyte sedimentation rate (ESR); B2 microglobulin and immunological markers. Markers monitored for stage 0/1 CLL were FBC, CRP and ESR, and immunological markers.

Results. Of 10 MGUS/SMM patients,5 (50%) were neutropenic at baseline, and the Curcuforte/Ribraxx combination therapy showed an increased neutrophil count, varying between 10% and 90% among 8 of the 10 (80%) MGUS/SMM patients. An additional benefit of the combination therapy was the potent effect in reducing the raised ESR in 4 (44%) of the MGUS/SMM patients.

Conclusion. Addition of Ribraxx to curcumin therapy may be of benefit to patients with early-stage B-cell lymphoid malignancies.

Disciplines

Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

Golombick, T., Diamond, T. H., Manoharan, A. & Ramakrishna, R. (2016). Addition of rice bran arabinoxylan to curcumin therapy may be of benefit to patients with early-stage B-cell lymphoid malignancies (monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or stage 0/1 chronic lymphocytic leukemia): a preliminary clinical study. Integrative Cancer Therapies, 15 (2), 183-189.

Integrative Cancer Therapies
January-March 2016: 1–7

DOI: 10.1177/1534735416635742
ict.sagepub.com
SAGE

Addition of Rice Bran Arabinoxylan to Curcumin Therapy May Be of Benefit to Patients With Early-Stage B-Cell Lymphoid Malignancies (Monoclonal Gammopathy of Undetermined Significance, Smoldering Multiple Myeloma, or Stage 0/1 Chronic Lymphocytic Leukemia): A Preliminary Clinical Study

Terry Golombick, PhD, Dipl Nut[1], Terrence H. Diamond, MB, BCh, MRCP, FRACP[1], Arumugam Manoharan, MD, FRACP, FRCPA[2], and Rajeev Ramakrishna, BMed, FRACP, FRCPA[2]

Abstract

Hypothesis. Prior studies on patients with early B-cell lymphoid malignancies suggest that early intervention with curcumin may lead to delay in progressive disease and prolonged survival. These patients are characterized by increased susceptibility to infections. Rice bran arabinoxylan (Ribraxx) has been shown to have immunostimulatory, anti-inflammatory, and proapoptotic effects. We postulated that addition of Ribraxx to curcumin therapy may be of benefit. *Study design*. Monoclonal gammopathy of undetermined significance (MGUS)/smoldering multiple myeloma (SMM) or stage 0/1 chronic lymphocytic leukemia (CLL) patients who had been on oral curcumin therapy for a period of 6 months or more were administered both curcumin (as Curcuforte) and Ribraxx. *Methods*. Ten MGUS/SMM patients and 10 patients with stage 0/1 CLL were administered 6 g of curcumin and 2 g Ribraxx daily. Blood samples were collected at baseline and at 2-month intervals for a period of 6 months, and various markers were monitored. MGUS/SMM patients included full blood count (FBC); paraprotein; free light chains/ratio; C-reactive protein (CRP)and erythrocyte sedimentation rate (ESR); B2 microglobulin and immunological markers. Markers monitored for stage 0/1 CLL were FBC, CRP and ESR, and immunological markers. *Results*. Of 10 MGUS/SMM patients,5 (50%) were neutropenic at baseline, and the Curcuforte/Ribraxx combination therapy showed an increased neutrophil count, varying between 10% and 90% among 8 of the 10 (80%) MGUS/SMM patients. An additional benefit of the combination therapy was the potent effect in reducing the raised ESR in 4 (44%) of the MGUS/SMM patients. *Conclusion*. Addition of Ribraxx to curcumin therapy may be of benefit to patients with early-stage B-cell lymphoid malignancies.

Keywords

curcumin, rice bran arabinoxylan, monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma (SMM), stage 0/1 chronic lymphocytic leukemia (CLL), early stage B-cell lymphoid malignancies

Submitted Date: 22 November 2015; Revised Date: January 24 2016; Acceptance Date: 25 January 2016

Introduction

Studies with patients with early B-cell lymphoid malignancies—that is, monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), or stage 0/1 chronic lymphocytic leukemia (CLL)—have been carried out in our clinics from 2010 to 2015. Our results

[1]St George Hospital, Sydney, Australia
[2]University of Wollongong, NSW, Australia

Corresponding Author:
Terry Golombick, Prichard Wing, St George Hospital, Prichard Wing, Gray Street, Kogarah, NSW 2217, Australia.
Email: terry.golombick@sesiahs.health.nsw.gov.au

suggest that early intervention with curcumin may lead to delay in progressive disease and prolonged survival in some of these patients.[1-6] Multiple myeloma and its precursor diseases—that is, MGUS/SMM—account for approximately 1% of neoplastic diseases and 13% of hematological cancers in Western countries.[7] CLL is the most common type of leukemia in the Western world.[8] Patients with early phases of these B-cell disorders are routinely monitored in a "watch and wait" modality. For these patients, a low risk of disease progression, the potential for drug-related toxicity, and the failure to achieve a complete remission does not justify conventional chemotherapy as a therapeutic option. They represent an excellent group to determine whether early intervention with nontoxic nutraceutical agents with known chemopreventive, anti-inflammatory, and/or immunostimulatory effects may be of benefit.

Patients with these early B-cell lymphoid malignancies are characterized by increased susceptibility to infections; in part, this results from a disruption in the normal processes for synthesis of immunoglobulins.[9] Typically, CLL patients exhibit impaired antibody production, often resulting in pan- or partial hypogammaglobulinemia. In multiple myeloma, the malignant plasma cells elaborate a single species of immunoglobulin and/or a monoclonal light chain. In contrast, the polyclonal antibody synthesis required for protection against bacterial infection is often impaired. Thus, these patients can be considered "functionally" hypogammaglobulinemic.[9]

A number of nutraceutical agents have been shown to have an immunostimulatory, anti-inflammatory, and/or proapoptotic effect, and combining their action with curcumin may be synergistic. Rice bran arabinoxylan (Ribraxx)—a proprietary formulation of rice bran and shitake mushroom extract—has been extensively studied and found to have immune stimulating, anti-inflammatory, and proapoptotic effects.[10-19]A clinical study by Cholujova et al[20] on 48 myeloma patients showed that Ribraxx, at a dose of 2 g/d, increased NK cell activity, increased the level of mDCs in the peripheral blood, and augmented levels of Th-1–related cytokines in the plasma of these patients compared with a placebo group. An invitro study by Ghoneum and Gollapudi[21] showed that Ribraxx and curcumin synergized in the induction of apoptosis of the U266 human multiple myeloma cell line. Based on the above findings, we proposed to recruit 10 patients with MGUS/SMM and 10 patients with stage 0/1 CLL who had been taking curcumin for a period of 6 months or more prior to the study and who had reached a stable response status as determined by markers of disease progression and administer both curcumin (as Curcuforte C3 complex) and Ribraxx in order to determine whether Ribraxx either induces or improves the clinical response.

Methods

A total of 10 MGUS/SMM patients (as defined by the International Myeloma Working Group) and 10 patients with stage 0/1 CLL with significant lymphocytosis ($>15\times10^9$lymphocytes/L) and Rai stage 0 (early CLL and lymphocytosis) or stage 1 (CLL and lymphadenopathy) were recruited. All the patients in the study had been on oral curcumin therapy (600mg to 6g daily) for a period of 6 months or more and had reached a stable disease response as determined by markers of disease progression. For the MGUS/SMM patients, this included paraprotein, total protein, free light chains, and percentage plasma cells; for the stage 0/1 CLLpatients, this included absolute lymphocyte count (ALC). All the patients in the study had provided written informed consent before study enrolment in accordance with the Declaration of Helsinki. The protocols for the curcumin studies with MGUS/SMM patients (ACTRN12610000962033) and the stage 0/1 CLL patients (ACTRN12615000487516) were reviewed and approved by the South Eastern Sydney and Illawarra ethics committee.

They were administered 6 g of curcumin (as Curcuforte, in a divided dose) and 2 g Ribraxx (in a divided dose) daily. Blood samples were collected at baseline and at 2-month intervals for a period of 6 months. Markers monitored for the MGUS/SMM patients included FBC, paraprotein, free light chains/ratio, C-reactive protein (CRP)and erythrocyte sedimentation rate (ESR), B2 microglobulin, and immunological markers, including serum immunoglobulins (sIgGs) and surface leukocyte markers. Markers monitored for stage 0/1 CLL were FBC, CRP and ESR, and immunological markers, including sIgGs and surface leukocyte markers.

Serum paraprotein and immunoglobulin-electrophoresis was determined by agarose gel (Sebia, Cedex, France); serum B2 microglobulin was measured using Beckman instruments (Beckman Instruments, Fullerton, CA); FLC analysis was performed by immunonephelometry using specific antibodies (the binding site) on a BNII nephelometer (Dade Behring, Deerfield, Illinois); CD4, CD8, and NK cell counts were determined by flow cytometry using Beckman instruments.

Curcumin (as Curcuforte) and Ribraxx were supplied by BioMedica Nutraceuticals.

Results

Monoclonal Gammopathy of Undetermined Significance/Smoldering Multiple Myeloma

A total of 10 patients were recruited—6 men and 4 women, with a mean age 68.5 years. Four patients diagnosed with IgA MGUS/SMM, 4 with IgG MGUS/SMM, and 2 with light chain disease (Table 1). All 10 patients completed the study. Two patients developed diarrhea on the combination therapy and stopped taking curcumin but continued with Ribraxx only (patients 3 and 9). One patient developed

Table 1. Patient Demographics.

Patient No.	Age	Sex	Paraprotein Type
MGUS/SMM			
1	55	M	IgAk
2	74	F	IgGk
3	62	M	IgGL
4	65	F	IgAk
5	70	M	Light chain disease
6	65	F	IgGk
7	65	M	IgAL
8	70	M	IgGL
9	73	M	Light chain disease
10	86	F	IgAk
Patient No.	**Age**	**Sex**	**Absolute Lymphocyte Count at Baseline (1×10^9/L to 4×10^9/L)**
Stage 0/1 CLL			
1	55	M	63.6
2	37	M	36.5
3	72	M	15.4
4	70	M	16.8
5	68	M	54.7
6	83	M	17.6
7	66	M	29.3
8	80	M	44.3
9	72	F	31
10	80	F	51.8

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; CLL, chronic lymphocytic leukemia.

abnormal liver function markers, stopped the curcumin therapy, and continued with Ribraxx only (patient 6).

During the 6-month study period, markers such as paraprotein, total protein, free light chains, B2 microglobulin, and CRP showed nonsignificant fluctuating levels (Table 2). A number of immunological markers were monitored over the 6-month study period (Table 3). The serum IgG, IgM, and IgA showed no significant changes, but the neutrophil count increased in 8/10 (80%) patients ($P< .05$, Table 4). Five of these patients (50%; patients 1,3,5,6,9) were neutropenic at baseline, and all demonstrated an increase in neutrophil count varying between 10% and 90% over the 6 months (Table 4). Patient 3, 6, and 9 were on Ribraxx only. Some of the patients with a normal baseline neutrophil count also showed an increase on the Curcuforte/Ribraxx combination therapy.

Of 9 MGUS/SMM patients,6 (67%) had an elevated ESR at baseline (Table 5; data not available for patient 6). Two patients (1 and 4) showed >80% reduction in their ESR levels at month 2 with combination therapy (Table 5); one of these (number 4) showed a subsequent increase in ESR,

Table 2. Mean (±SD) Values of Paraprotein, Total Protein, ESR, and CRP in MGUS/SMM Patients Over the 6-Month Study Period.

	Baseline	Month 2	Month 4	Month 6
Paraprotein[a]	23.6 ± 12.8	26.9 ± 19.3	24.4 ± 17.1	27.6 ± 20.7
Total protein[b] (64-83 g/L)	80.2 ± 15.9	81.2 ± 20.4	78.4 ± 17.2	82.2 ± 21.8
ESR[b] (1-20 mm/h)	50.3 ± 44.5	27.9 ± 17.5	42.3 ± 35.9	45.6 ± 41.7
CRP[b] (0-5 mg/L)	4.6 ± 6.1	4.0 ± 4.7	4.6 ± 6.1	5 ± 5

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma.
[a]n=8.
[b]n=10.

Table 3. Mean (±SD) Values of Immunological Markers in the 10 MGUS/SMM Patients Over the 6-Month Study Period.

	Baseline	Month 2	Month 4	Month 6
Neutrophil (2×10^9/L to 7×10^9/L)	2.8 ± 2	3.3 ± 1.9	3.5 ± 2.4	3.3 ± 1.8
IgG (6.2-14.4g/L)	14.6 ± 13.2	14.5 ± 13.9	14.1 ± 13.1	14.9 ± 14.1
IgA (0.6-3.96 g/L)	10.1 ± 16.1	11 ± 17.9	10.7 ± 19.0	12.6 ± 21.9
IgM 0.48-3.04 g/L	0.29 ± 0.18	0.27 ± 0.18	0.27 ± 0.16	0.27 ± 0.19
CD4[a] (0.4×10^9/L to 1.4×10^9/L)	0.79 ± 0.49	0.93 ± 0.58	0.71 ± 0.3	0.79 ± 0.39
CD8[a] (0.2×10^9/L to 0.9×10^9/L)	0.27 ± 0.13	0.31 ± 0.13	0.28 ± 0.17	0.33 ± 0.19
NK[a] (0.05×10^9/L to 0.6×10^9/L)	0.31 ± 0.16	0.32 ± 0.14	0.25 ± 0.12	0.29 ± 0.18

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; NK, natural killer cells.
[a]n=9.

whereas patient 1 maintained a >80% decrease at 6 months. Two patients (9 and 10) showed a >20% reduction in ESR from baseline at 6 months (Table 5).

CD4 and CD8 T-cell counts were available for 9/10 MGUS/SMM patients during the course of the study (data not available for patient 6; Tables 6 and 7). Seven of these (77%) had normal baseline CD4 and CD8 counts (CD4 = 0.4×10^9/L to 1.4×10^9/L; CD8 = 0.2×10^9/L to 0.9×10^9/L). Whereas most patients showed fluctuating counts during the course of the study, patients 1,7, and 10 showed a >40% increase in CD4 and CD8 T-cell numbers at the end of the

Table 4. Individual Neutrophil Counts[a] Over the 6-Month Study Period.

Patient Number	Baseline	Month 2	Month 4	Month 6	Percentage Change From Baseline
MGUS/SMM					
1	0.89	0.62	1.04	1.44	62
2	6.41	6.67	7.1	4.77	−25
3[b]	1.91	2.84	2.83	2.47	29
4	2.26	2.88	8.07	3.08	36
5	0.94	2.52	1.17	1.72	83
6[b]	1.7	1.6	1.9	1.9	12
7	3.4	3.7	3.4	6.4	88
8	4.74	5.17	4.05	5.45	15
9[b]	0.83	1.68	1.3	1.52	83
10	4.99	4.84	3.85	4.48	−10
Stage 0/1 CLL					
1	5.16	8.21	4.91	6.08	18
2	9.1	5.87	4.59	5.32	−42
3	4.6	4.13	5.55	3.75	−19
4	3.05	2.89	2.55	3.52	15
5	3.8	3.9	3.4	2.9	−24
6	4.5	4.9	4.1	4.42	−2
7[b]	4.52	5.69	4.31	5.13	13
8	2.2	6.3	5.04	7.56	244
9	2.94	2.26	2.33		−21

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; CLL, chronic lymphocytic leukemia.
[a]Normal =2×10^9/Lto 7×10^9/L
[b]Ribraxx only.

Table 5. Individual ESR Values[a] in MGUS/SMM Patients Over the 6-Month Study Period.

Patient Number	Baseline	Month 2	Month 4	Month 6	Percentage Change From Baseline
1	130	24	7	11	–92
2	43	34	36	84	95
3[b]	10	25	16	12	20
4	106	2	105	117	10
5	5	7	7	7	40
7	4	30	26	18	350
8	59	62	64	91	54
9[b]	63	39	90	50	−21
10	33	28	30	20	–39

Abbreviations: ESR, erythrocyte sedimentation rate; MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma.
[a]Normal = 1-30mm/h.
[b]Ribraxx only.

6-month study period (Tables 6 and 7). NK cell counts fluctuated over the course of the study but showed no significant changes (Tables 3 and 8).

Table 6. Individual CD4 T-cell Counts[a] Over the 6-Month Study Period.

Patient Number	Baseline	Month 2	Month 4	Month 6	Percentage Change From Baseline
MGUS/SMM					
1	0.42	0.36	0.52	0.63	50
2	1.64	2.2	1.2	1.45	–12
3[b]	0.64	0.76	0.76	0.7	9
4	1.46	1.27	0.75	1.18	–19
5	1	1.02	0.66	0.83	–17
7	0.47	1.06	0.98	0.85	81
8	0.82	0.95	0.9		10
9[b]	0.38	0.38	0.18	0.18	–53
10	0.3	0.41	0.47	0.51	70
Stage 0/1 CLL					
1	5.09	3.01	1.7	4.84	–5
2	1.46	3.54	1.55	1.55	6
3	0.92	1.18	1.21		32
4	1.34	0.86	1.28	1.06	–21
5	1.64	1.83	1.49	1.71	4
6	3.22	3.04	1.95	2.38	–26
7[b]	2.22	3.32	2.48	2.06	–7
8	2.93	2.93	3.61	4.04	38
9	5.18	3.82	2.96		–43

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; CLL, chronic lymphocytic leukemia.
[a]Normal = 0.4×10^9/Lto 1.4×10^9/L.
[b]Ribraxx only.

Stage 0/1 CLL

A total of 10 stage 0/1 CLL patients with an ALC>15×10^9/L (normal = 1×10^9/L to 4×10^9/L) were recruited into the study. There were 8 men and 2 women, with a mean age of 68 years (Table 1). One patient withdrew because of difficulties with administering the large number of tablets, and 1 patient developed severe diarrhea and was administered Ribraxx only (patient 7).Mean values of the various hematological markers (FBC, CRP and ESR, sIgGs, and surface leukocyte markers) over the course of the study are shown in Table 9.

Whereas most patients showed fluctuating ALCs (Table 10), patient number 6 showed a 42% decrease in ALC over the 6 months while on the Curcuforte/Ribraxx therapy, and patient number 9 showed a 29% decrease in ALC but withdrew because of shingles, which developed at 4 months after the combination therapy.

Neutrophil counts of all 9 patients with stage 0/1 CLL were normal at baseline (Table 4). One patient (number 8) showed an increase in neutrophil count over the 6 months, whereas the remaining 8 patients showed stable or fluctuating neutrophil counts, with no significant change. There was no significant change in the sIgGs—that is, IgG, IgM, and IgA—over the study period (Table 9).

Table 7. Individual CD8 T-cell Counts[a] Over the 6-Month Study Period.

Patient Number	Baseline	Month 2	Month 4	Month 6	Percentage Change From Baseline
MGUS/SMM					
1	0.48	0.41	0.59	0.69	44
2	0.37	0.5	0.23	0.28	–24
3[b]	0.26	0.3	0.24	0.23	–12
4	0.29	0.24	0.18	0.26	–10
5	0.15	0.26	0.13	0.2	33
7	0.04	0.06	0.05	0.12	200
8	0.27	0.27	0.26		–4
9[b]	0.34	0.34	0.35	0.35	3
10	0.27	0.44	0.51	0.51	89
Stage 0/1 CLL					
1	2.54	1.81	1.13	2.76	9
2	0.37	1.33	0.52	0.52	41
3	0.46	1.18	1.21		163
4	1.18	0.57	0.96	1.06	–10
5	1.64	1.83	1.49	1.71	4
6	1.76	2.21	0.98	1.19	–32
7[b]	1.33	1.9	1.98	1.03	–23
8	1.6	1.6	2.17	2.18	36
9	1.55	1.27	1.48		–5

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; CLL, chronic lymphocytic leukemia.
[a]Normal = 0.2×10^9/Lto 0.9×10^9/L.
[b]Ribraxx only.

Table 8. Individual NK Cell Counts[a] Over the 6-Month Study Period.

Patient Number	Baseline	Month 2	Month 4	Month 6	Percentage Change From Baseline
MGUS/SMM					
1	0.38	0.34	0.36	0.48	26
2	0.5	0.47	0.17	0.23	–54
3[b]	0.06	0.06	0.06	0.04	–33
4	0.34	0.5	0.42	0.58	71
5	0.44	0.34	0.25	0.41	–7
7	0.18	0.25	0.14	0.18	0
8	0.48	0.44	0.41		–15
9[b]	0.25	0.25	0.2	0.2	–20
10	0.14	0.24	0.22	0.18	29
Stage 0/1 CLL					
1	2.54	1.2	1.13	2.07	–19
2	1.46	2.66	1.03		–30
3	0.31	0.94	0.91		194
4	1.01	0.72	0.96	1.06	5
5	0.55	0.61	0.5	0.57	4
6	1.17	1.1	0.39	0.51	–56
7[b]	1.33	0.95	0.99	1.03	–22
8	0.81	0.8	0.72	0.93	15
9	2.07	2.12	1.85		–11

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; CLL, chronic lymphocytic leukemia; NK, natural killer cells.
[a]Normal = 0.05×10^9/Lto 0.6×10^9/L.
[b]Ribraxx only.

Baseline CD4, CD8 T-cell, and NK cell counts were elevated in 7/9 (78%) of stage 0/1 CLL patients, in accordance with previous findings (Tables 6-8). Most showed fluctuating counts during the study, with patient numbers 3 and 8 demonstrating an increase in CD4, CD8, and NK cell counts after 6 months (Tables 6-8).

Discussion

Previous curcumin studies with early B-cell lymphoid malignancies have shown an improvement in disease markers in some patients.[1-6] The addition of Ribraxx to curcumin therapy in patients who have reached a stable disease response does not appear to change this response but may have a positive clinical impact in the MGUS/SMM subset by increasing neutrophil counts and decreasing inflammation as determined by an improvement in the ESR.

Neutropenia is a common and serious complication in multiple myeloma and patients with early-stage disease. A neutropenic patient is at significant risk of bacterial or fungal infections.[22] The addition of Ribraxx to the curcumin administration appears to have been effective in increasing the neutrophil count in both the neutropenic MGUS/SMM patients and the patients with normal baseline neutrophil counts. This study is the first to show such positive effects of Ribraxx.

Whereas MGUS/SMM and stage 0/1 CLL both represent early B-cell lymphoid malignancies, patients present with different hematological and biochemical features. In multiple myeloma of the IgG and IgA subtypes, significant correlations have been found between ESR and the monoclonal proteins and between the ESR and percentageof plasma cells in bone marrow.[23] Alexandrakis et al[24] suggest that ESR is an independent prognostic factor for survival in patients with MM. Patients with earlier-stage disease may also show elevated levels of this acute phase protein, as evident by the raised ESR in our MGUS/SMM cohort. The Curcuforte/Ribraxx combination therapy showed a potent effect in reducing the raised ESR in 2 of 9 (22%) patients at month 2. This fall in ESR, despite no change in the paraprotein level, was an unexpected finding, perhaps resulting from a synergism in anti-inflammatory activity of both curcumin and Ribraxx. One of these patients maintained the dramatic decrease in ESR.

Ribraxx has been previously shown to enhance NK cell–mediated cytotoxicity but not increase NK cell number.[10,11]

Table 9. Hematological Markers (Mean±SD) in Stage 0/1 CLL Patients Over the 6-Month Study Period.

	Baseline (n = 9)	Month 2 (n = 9)	Month (n = 9)	Month 6
ALC (1×10^9/L to 4×10^9/L)	38.2 ± 16.8	38.6 ± 16.5	38.4 ± 14.5	41 ± 18.2
Neutrophil (2×10^9/L to 7×10^9/L)	4.4 ± 2	4.9 ± 1.8	4.1 ± 1.1	4.8 ± 1.5
IgG (6.2-14.4 g/L)	8.47 ± 0.3	8.08 ± 2.3	8.12 ± 2.4	7.9 ± 3.2[a]
IgA (0.6-3.96 g/L)	1.3 ± 0.6	1.3 ± 0.6	1.23 ± 0.5	1.3 ± 0.5[a]
IgM (0.48-3.04 g/L)	0.32 ± 0.2	0.37 ± 0.4	0.28 ± 0.2	0.27 ± 0.18[a]
CD4 (0.4×10^9/L to 1.4×10^9/L)	2.67 ± 1.6	2.61 ± 1.1	2.03 ± 0.8	2.52 ± 1.4[a]
CD8 (0.2×10^9/L to 0.9×10^9/L)	1.38 ± 0.7	1.52 ± 0.5	1.32 ± 0.5	1.5 ± 0.8[a]
NK (0.05×10^9/L to 0.6×10^9/L)	1.25 ± 0.7	1.23 ± 0.7	0.94 ± 0.4	1.03 ± 0.6[a]

Abbreviations: CLL, chronic lymphocytic leukemia; ALC, absolute lymphocyte count; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; NK, natural killer cells.
[a]n=6.

Table 10. Individual ALC Counts[a] in Stage 0/1 CLL Patients Over the 6-Month Study Period.

Patient Number	Baseline	Month 2	Month 4	Month 6	Percentage Change From Baseline
1	63.58	60.19	56.49	69.13	9
2	36.5	44.27	51.58	47.88	31
3	15.35	23.6	30.34	33	115
4	16.77	14.31	16.03	21.21	26
5	54.7	60.9	49.5	57	4
6	29.32	27.59	19.52	17.02	−42
7[b]	44.32	47.4	49.49	51.36	16
8	31	26.6	36.09	31.05	0.16
9	51.84	42.37	36.96		−29

Abbreviations: ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukemia.
[a]Normal = 1×10^9/Lto 4×10^9/L.
[b]Ribraxx only.

Our study confirms these findings in the MGUS/SMM patients treated with the Curcuforte/Ribraxx combination therapy. However, cellactivation studies were not carried out.

Immunomodulation of CD4 T-cell, CD8 T-cell, and NK cell subsets has been previously shown following curcumin therapy.[25-28] CD8 cytotoxic T lymphocytes are involved in antigen-specific tumor destruction, and CD4 T-cells are essential for helping the CD8 T-cell–dependent tumor eradication.[25] A study by Ghoneum and Agrawal[29] demonstrated that Ribraxx enhances the generation of cytotoxic CD8 T-cells. Because of the combination therapy of Curcuforte/Ribraxx, the percentage of CD4 and CD8 T-cells increased in 3 of 9 (33%) patients in the MGUS/SMM group.

Our previous study with stage 0/1 CLL patients and Meriva curcumin[6] found that 20% of patients demonstrated >20% decrease in ALC over 6 months. This decrease in ALC was accompanied by an increase in CD4, CD8, and NK cells. In the present study, Meriva curcumin was replaced by C3-complex Curcuforte, and Ribraxx was added to the regimen and showed a similar result, where 2 of 9 (22%) early CLL patients show a >20% decrease in ALC at 6 months. A study by Ghoneum and Gollapudi[14] showed that Ribraxx sensitizes the human leukemic HUT 78 cell line to death receptor (CD95)-induced apoptosis, perhaps providing a mechanism of clinical activity seen in these patients. As a result of the combination therapy with Curcuforte/Ribraxx, the percentage of CD4 and CD8 T-cells increased in 2 of 9 (22%) patients in the stage 0/1 CLL group.

In conclusion, the addition of Ribraxx to curcumin therapy may be valuable because of its ability to improve the clinical response in the MGUS/SMM patients through an increase in neutrophil count and a decrease in inflammation as determined by ESR and its immunomodulatory effect on CD4, CD8, and NK cells. Similarly stage 0/1 CLL patients may benefit through the combined immunomodulatory activity of both curcumin and Ribraxx and the proapoptotic effect of Ribraxx.

Our pilot study has the limitation of only a small number of patients in both groups. A larger randomized, placebo-controlled study is recommended to further explore the value of Curcuforte/Ribraxx combination therapy in patients with early B-cell lymphoid malignancies

Authors' Note

The curcumin trials were registered with the Australian New Zealand Clinical Trials Registry (ANZCTR).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Terry Golombick received partial funding support during the study period. The other authors received no financial support. The publication costs are borne by Biomedica.

References

1. Golombick T, Diamond T. The potential role of curcumin (diferuloylmethane) in plasma cell dyscrasias/paraproteinemia. *Biologics*. 2008;2:161-163.

2. Golombick T, Diamond T, Badmaev, et al. The potential role of curcumin in patients with monoclonal gammopathy of undefined significance: its effect on paraproteinemia and the urinary N-telopeptide of type 1 collagen bone turnover marker. *Clin Cancer Res*. 2009;15:5917-5922.
3. Golombick T, Diamond T, Manoharan A, Ramakrishna R. Monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM) and curcumin: a randomised, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study. *Am J Hematol*. 2012;87:455-460.
4. Golombick T, Diamond T, Manoharan A, Ramakrishna R. Long term use of curcumin in two smoldering multiple myeloma patients. *J Hematol Malig*. 2013;3:18-23.
5. Golombick T, Diamond T, Manoharan A, Ramakrishna R. Stabilisation of laryngeal AL amyloidosis with long term curcumin therapy: a case report. *Case Rep Hematol*. 2015;(2015):910528.
6. Golombick T, Diamond T, Manoharan A, Ramakrishna R. The effect of curcumin (as Meriva) on absolute lymphocyte count (ALC), NK cells and T cell populations in patients with stage 0/1 chronic lymphocytic leukemia. *J Cancer Ther*. 2015;6:566-571.
7. Palumbo A, Anderson MD. Multiple myeloma. *N Engl J Med*. 2011;364:1046-1060.
8. Huergo-Zapico L, Acebes-Huerta A, Gonzalez-Rodriguez AP, et al. Expansion of NK cells and reduction of NKG2D expression in chronic lymphocytic leukemia: correlation with progressive disease. *PLoS One*. 2014;9(10):1-9.
9. Winkelstein A, Jordan SP. Immune deficiencies in chronic lymphocytic leukemia and multiple myeloma. *Clin Rev Allergy*. 1992;10:39-58.
10. Ghoneum M, Abedi S. Enhancement of natural killer cell activity of aged mice by modified arabinoxylan rice bran (MGN-3/Biobran). *J Pharm Pharmacol*. 2004;56:1581-1588.
11. Ghoneum M. Enhancement of human natural killer cell activity by modified arabinoxylan from rice bran (MGN-3). *Int J Immunother*. 1998;14:89-99.
12. Bang MH, Van Riep T, Thinh NT, et al, Arabinoxylan rice bran (MGN-3) enhances the effects of interventional therapies for the treatment of hepatocellular carcinoma: a three-year randomized clinical trial.*Anticancer Res*. 2010;30:5145-5151.
13. Gollapudi S, Ghoneum M. MGN-3/Biobran, modified arabinoxylan from rice bran, sensitizes human breast cancer cells to chemotherapeutic agent, daunorubicin. *Cancer Detect Prev*. 2008;32:1-6.
14. Ghoneum M, Gollapudi S. Modified arabinoxylan rice bran (MGN-3/Biobran) sensitizes human T cell leukemia cells to death receptor (CD95)-induced apoptosis. *Cancer Lett*. 2003;201:41-49.
15. Ghoneum M, Gollapudi S. Synergistic role of arabinoxylan rice bran (MGN-3/Biobran) in *S. cerevisiae*–induced apoptosis of monolayer breast cancer MCF-7 cells. *Anticancer Res*. 2005;25:4187-4196.
16. Ghoneum M, Badr El-Din NK, Ali DA, El-Dein MA. Modified arabinoxylan from rice bran, MGN-3/biobran, sensitizes metastatic breast cancer cells to paclitaxel in vitro. *Anticancer Res*. 2014;34:81-87.
17. Ghoneum M, Matsuura M. Augmentation of macrophage phagocytosis by modified arabinoxylan rice bran (MGN-3/biobran). *Int J Immunopathol Pharmacol*. 2004;17:283-292.
18. Ghoneum M, Matsuura M, Gollapudi S. Modified arabinoxylan rice bran (MGN-3/Biobran) enhances intracellular killing of microbes by human phagocytic cells in vitro. *Int J Immunopathol Pharmacol*. 2008;21:87-95.
19. Ghoneum M, Jewett A. Production of tumor necrosis factor-alpha and interferon-gamma from human peripheral blood lymphocytes by MGN-3, a modified arabinoxylan from rice bran, and its synergy with interleukin-2 in vitro. *Cancer Detect Prev*. 2000;24:314-324.
20. Cholujova D, Jakubikova J, Czako B, et al. MGN-3 arabinoxylan rice bran modulates innate immunity in multiple myeloma patients. *Cancer Immunol Immunother*. 2013;62:437-445.
21. Ghoneum M, Gollapudi S. Synergistic apoptotic effect of arabinoxylan rice bran (MGN-3/Biobran) and curcumin (turmeric) on human multiple myeloma cell line U266 in vitro. *Neoplasma*. 2011;58:118-123.
22. Hillman RS, Ault KA, Rinder H. *Hematology in Clinical Practice*. 4th ed. New York, NY: McGraw-Hill; 2005.
23. Talstad I, Haugen HF. The relationship between the erythrocyte sedimentation rate (ESR) and plasma proteins in clinical materials and models. *Scand J Clin Lab Invest*. 1979;39:519-524.
24. Alexandrakis MG, Passam FH, Ganotakis ES, et al. The clinical and prognostic significance of ESR, serum interleukin-6 and acute phase protein levels in multiple myeloma. *Clin Lab Haematol*. 2003;25:41-46.
25. Varalakshmi AC, Mubarak A, Pardhasaradhi BVV, et al. Immunomodulatory effects of curcumin: in-vivo. *Int Immunopharmacol*. 2008;8:688-700.
26. Aggarwal BB, Kumar A, Aggarwal MS, Shisodia S. Curcumin derived from turmeric *Curcuma longa*: a spice for all seasons. *Phytopharm Cancer Chemoprev*. 2005:349-387.
27. Chang Y-F, Chuang H-Y, Hsu C-H, et al. Immunomodulation of curcumin on adoptive therapy with T cell functional imaging in mice. *Cancer Prev Res*. 2011;5:444-452.
28. Bhattacharyya S, Hossain DMS, Mohanty S, et al. Curcumin reverses T cell-mediated adaptive immune dysfunctions in tumor-bearing hosts. *Cell Mol Immunol*. 2010;7:306-315.
29. Ghoneum M, Agrawal S. MGN-3/Biobran enhances generation of cytotoxic CD8+ T cells via upregulation of Dec-205 expression on dendritic cells. *Int J Immunopathol Pharmacol*. 2015;4:523-530.