

Beneficial Roles of Histone Deacetylase Inhibitor Butyrate to Multiple Myeloma, Acute Leukemia and Acute Myeloid Leukemia: Case Reports

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ABSTRACT

Multiple myeloma (MM) belongs to hematological malignancy that derives pro-survival/proliferative signals from the bone marrow niche, and its incidence is increasing worldwide. Butyrate, a well-known epigenetic histone deacetylase inhibitor, reduces the viability of MM cells, induces MM cell apoptosis via transcriptional activation of p21. In present review we discuss butyrate as a potential therapeutic drug for MM and case reports of MM, acute leukemia, malignant lymphoma and glioma patients.

Key words: Histone deacetylase inhibitor butyrate; Multiple myeloma; Hematological malignancy; Case reports; Aloe vera adjuvant

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INTRODUCTION

Diet is a natural source of butyrate (sodium butyrate: NaOOCCH₂CH₂CH₃) through the fermentation of non-digestive fiber such as polysaccharide; acemannan (ACM) in aloe vera gel, is a strong appealing target for health and quality of life as an immune modulation and colorectal cancer prevention in aged people. Identification of butyrate-producing endophytic microbiota in aloe vera gel fermentation and finding of anti-inflammatory as well as antioxidant activities of butyrate in the fermented gel may help explain the known beneficial effects of butyrate in intestinal colon and on colitis^[1]. Butyrate has been shown to affect various cancer cells. Butyrate exerts its anti-cancerous effects by several mechanisms and has led to successful outcomes in phase I and II clinical trials. Butyrate has been shown to exhibit the protective effect on inflammatory diseases^[2]. A novel immune-enhancing polysaccharides and importance of gut microbiota inducing gut immunity are discussed on basis to apply the aloe vera ACM; ACM as an immune adjuvant biological properties and an immunomodulatory in cat and chicken^[3].

Boonyagul *et al*^[4] investigated bone formation of ACM in a tooth extraction rat model. Primary rat bone marrow stromal cells (BMSCs) were treated with various concentrations of ACM. Bone formation was evaluated by dual-energy X-ray absorptiometry and histopathological examination. The *in vitro* results revealed ACM significantly increased BMSCs proliferation, VEGF, BMP-2, alkaline phosphatase activity, bone sialoprotein and osteopontin expression,

and mineralization. *In vivo* results showed ACM-treated groups had higher bone mineral density and faster bone healing compared with untreated controls. These data suggest ACM could function as a bioactive molecule inducing bone formation by stimulating BMSCs proliferation, differentiation into osteoblasts, and extracellular matrix synthesis. ACM could be a candidate natural biomaterial for bone regeneration. Our earlier paper^[5] showed that ACM as a nutraceutical aloe vera gel scaffolds, promotes soft tissue organization in biomedical applications and polymeric matrix. ACM can induce a much-controlled release of active ingredients and be used as bio-functional scaffolds in a biodegradable form. Furthermore, we conducted to compare effects of ACM and formocresol as pulp-dressing agents clinically and radiographically in primary teeth, and showed higher clinical and radiographic success rate compared to formocresol as a pulpotomy agent in molars. ACM can be considered as an acceptable biomaterial for vital pulp therapy of deep caries in primary teeth^[6].

Many studies have documented the capability of epigenetic regulators from dietary sources to modulate gene expression in cancer cells through covalent modification of DNA as well as histone and non-histone proteins. Histone acetyltransferases and histone deacetylases (HDACs) are among the most studied targets for chromatin remodeling, control of gene expression, and anticancer therapy. Butyrate, a well-known epigenetic HDAC inhibitor, is causally implicated in tumorigenesis and tumor angiogenesis. Butyrate was shown to induce cell cycle arrest, differentiation, and apoptosis in a variety of cancer cells. In an earlier^[7] paper we discussed aloe vera fermentation as a tumor-suppressive process generating microbial-derived butyrate.

Multiple myeloma (MM) is an incurable cancer that derives pro-survival/proliferative signals from the bone marrow niche. It has been reported that myeloma cell-induced disruption of the highly organized bone marrow components both cellular and extracellular results in destruction of the marrow and support for MM cell proliferation, survival, and migration. Epigenetic regulation is closely associated with progression of MM. Histone deacetylases (HDACs) are crucial regulators of gene expression that function through histone modification, and HDAC inhibitor sodium butyrate functions in various physiologic processes, including inflammation and differentiation. We describe beneficial effect of butyrate to MM and show case reports in the treatment of MM, acute leukemia, malignant lymphoma and malignant glioma.

HISTONE DEACETYLASE INHIBITOR BUTYRATE IN THE TREATMENT OF MULTIPLE MYELOMA

Epigenetic regulation is closely associated with progression of MM. HDAC inhibitor butyrate functions in various physiologic processes, including inflammation and differentiation.

Butyrate suppresses cell proliferation and induces apoptosis by targeting p21 in multiple myeloma

Yao *et al.*^[8] reported that butyrate decreased survival of several human MM cell lines in a dose- and time-dependent manner. Butyrate reduces the viability of MM cells, and leads to cell cycle arrest at the G2/M phase in a dose-dependent manner. Butyrate induced MM cell apoptosis via transcriptional activation of p21 (cyclin-dependent kinase-inhibitor), suggesting that butyrate as a potential therapeutic drug for MM.

Chen *et al.*^[9] reviewed crosstalk of signaling pathways under butyrate influence. Butyrate can inhibit vascular endothelial growth factor (VEGF) through HDACs, which results in decreased VEGFR-mediated angiogenesis. Decreased VEGF leads to decreased cell-cycle/cell proliferation mediated by protein kinase B (Akt) and metastasis by its receptor neuropilin 1. Decreased Akt results in increased Bcl-2-associated X-protein/B cell lymphoma 2 ratio and thus increased apoptosis. Decreased Akt could also contribute decreased IL-6 and IL-17 by butyrate. Inhibition of HDACs and inflammation by butyrate results in decreased activity of the signal transducer and activator of transcription 3 pathway, which also contributes to cell proliferation, survival and metastasis through its downstream. Butyrate can act in multiple signaling pathways which facilitate blockage of such a feed-forward effect. This could be an advantage of butyrate in anti-cancer use.

IL-17-producing cells induced by gut microbiota favor multiple myeloma progression

The gut microbiota has been causally linked to cancer and multiple myeloma (MM). Calcinotto *et al.*^[10] provided evidence implying that *Provetella heparinolytica* promotes the differentiation of Th17 cells colonizing the gut and migrating to the bone marrow (BM) of transgenic Vk*MYC mice, where they favor progression of MM. Lack of IL-17 in Vk*MYC mice, or disturbance of their microbiome delayed MM appearance. Similarly, in smoldering MM patients, higher levels of BM IL-17 predicted faster disease progression. IL-17 induced signal transducer and activator of transcription (STAT) 3-phosphorylation in murine plasma cells, and activated eosinophils. Thus commensal bacteria in Vk*MYC mice appear to unleash a paracrine signaling network between adaptive and innate immunity that accelerate progression to MM. A selected microbiota locally favors the expansion of Th17 cells, which migrate to the BM niche, where they further contribute to the eosinophil-Th17-MM cells network.

A Molecular mechanism underlining anti-multiple myeloma effect of histone deacetylase 3 targeting in bone marrow stromal cells

Multiple myeloma (MM) is an incurable cancer that derives pro-survival/proliferative signals from the bone marrow (BM) niche. Ho *et al.*^[11] investigated the effects of HDAC3 targeting in bone marrow stromal cells (BMSCs). Using both BMSC lines as well as patient-derived BMSC3, the authors show that HDAC3 expression in BMSCs can be induced by co-culture with MM cells. Furthermore, the authors identified both quantitative and qualitative changes in exosomes and exosomal miRNA, as well as inhibition of IL-6 trans-signaling, as molecular mechanisms mediating anti-MM activity. The authors showed that HDAC3-knock-down in BM endothelial cells decreases neo-angiogenesis, consistent with a broad effect of HDAC3 targeting the BM-niche. The results support the clinical development of HDAC3 inhibitors based not only their direct anti-MM effects, but also their modulation of the BM microenvironment. HDACs are therapeutic targets in MM and HDACs inhibition decreases MM proliferation both alone and in co-culture with BMSC.

Interweaving the bone marrow microenvironment, bone loss, and multiple myeloma with interleukin-6

The immune system is strongly linked to the maintenance of healthy bone. Inflammatory cytokines, specifically, are crucial to skeletal homeostasis and any dysregulation can result in detrimental health complications. Interleukin, such as IL-6 act as osteoclast

differentiation modulators, encourages osteoclastogenesis when bound to progenitors and can cause excessive osteoclastic activity and osteolysis when overly abundant. The roles of IL-6 in the progression of MM are discussed by Harmer *et al.*^[12], including roles in bone homing, cancer-associated bone loss, disease progression and drug resistance. The authors discussed actions of IL-6 in the diseased bone marrow microenvironment and myeloma cells alter bone marrow adipocytes to make a more supportive niche for tumor cells and to increase osteoclastic activity through IL-6 and other molecules.

BENEFICIAL ROLES OF GUT MICROFLORA FOR CANCER IMMUNE THERAPY: CANCER IMMUNE CHECKPOINT INHIBITOR THERAPY AND THE GUT MICROBIOTA

The anti-cancer effect of butyrate has been demonstrated in cancer cell cultures and animal models of cancer. Butyrate, as a signal molecule, has effects on multiple signaling pathways. The most studied effect is its inhibition on HDAC, which leads to alterations of several important oncogenic signaling pathways such as Janus kinase 2/signal transducer and activator of transcription 3, vascular endothelial growth factor.

Cancer immune checkpoint inhibitor therapy and the gut microbiota

The past decade has seen tremendous advances in both our understanding of cancer immunosuppressive microenvironments and colonic bacteria facilitated by immune check point inhibitor antibodies and next generation sequencing, respectively. Because an important role of the host immune system is to communicate with and regulate the gut microbiota community, it should not come as a surprise that the behavior of one is coupled to the other. Frankel *et al.*^[13] attempted to dissect some of the studies demonstrating cancer immunotherapy modulation by specific gut microbes (*Bifidobacterium lactobacillus/Akkermanisia muciniphilla*) and discuss possible molecular mechanisms for this effect. The author proposed bacterial species producing SCFAs, butyrate, associated with enhancement immune checkpoint inhibitor therapy in human. Hidaka *et al.*^[14] investigated the association of plasma C-peptide, a surrogated marker of insulin and glycated albumin (GA), a more stable marker of blood glucose, with all-site and site-specific cancer risk by mutually according for their confounding effects. The study was prospectively conducted with nearly 4,000 cancer cases arising in the population-based cohort of 33,736 subjects who answered the baseline questionnaire and supplied blood samples. After exclusion of subjects with apparent diabetes mellitus (DM), analysis was done in 3,036 cancer cases and 3,667 sub-cohort subjects. Higher insulin levels, independently of higher blood glucose levels, may be relevant to DM-related carcinogenesis for several cancer sites. Examination of circulating insulin levels is a plausible option in evaluating cancer risk even in individuals who have not developed DM.

It is becoming clear that myeloma cell-induced disruption of the highly organized bone marrow components (such as cellular and extracellular) results in destruction of the marrow and support for multiple myeloma (MM) cell proliferation, survival, migration, and drug resistance. Proteasome inhibitors (PIs) have become increasingly common for treatment of MM and are currently an essential part of any anti-myeloma combination therapy. Farrell *et al.*^[15] discussed the mechanism of PI resistance in myeloma cells, and introduced briefly cell-autonomous and stress-mediated mechanisms

of PI resistance in MM.

ROLE OF HISTONE DEACETYLASE ISOFORMS IN MULTIPLE MYELOMA

Multiple myeloma (MM), which is derived immunoglobulin-producing plasma cells, is treated using novel agents, such as proteasome inhibitors. Histone deacetylase (HDAC) are a group of deacetylase enzymes that catalyze the deacetylation of histone and non-histone proteins, leading to changes in gene expression and protein function and stability. To maintain or argument anti-MM effects without severely adverse reactions, preclinical and clinical studies are being undertaken to elucidate the impact of each HDAC isoform on MM and develop class- or isoform-selective HDAC inhibitors in combination with other therapeutics. Harada^[16] reviewed role of HDAC isoforms and development in treatment of MM based on clinical findings.

Minimal residual disease negativity as a clinically relevant end point in the development of modern therapy for multiple myeloma

Patients with MM who achieve minimal residual disease (MRD) negativity after upfront treatment had superior outcomes compared with those remain MRD⁺. Recently, associations have been shown between specific commensal microbes and development of plasma cell disorders.

Pianko *et al.*^[17] reported the association between intestinal microbiota composition and treatment outcome in MM. Microbiota composition of fecal samples collected from 34 MM patients after induction therapy and at the time of flow cytometry-based bone marrow MRD testing was determined by 16S ribosomal RNA sequencing. The authors observed a high relative abundance of *Eubacterium hallii* in the 16 MRD patients relative to the 18 MRD⁺ patients. *E. hallii* and *Faecalibacterium prausnitzii* were identified in LeFse analysis and present in ≤ 10 patients. *F. prausnitzii* is a common butyrate-producing commensal microbe often associated positively with human gut health. In patients with a MRD⁻ treatment response, the authors found a higher abundance of the butyrate producer *E. hallii*. Butyrate is known to inhibit in vivo production of IL-17A via downregulation of Th-17 cells in human peripheral blood mononuclear cells. Of note, IL-17-producing Th-17 cells induced by microbiota have been associated with disease pathogenesis in a murine MM model, and after bone marrow transplantation, promotion of MM immune escape is mediated by donor-derived IL-17A. The results are novel and support the concept that intestinal microbiota composition is associated with deep treatment response. The potential association of microbiota composition with treatment response in MM patients is an important parameter for additional correlative and clinical investigation. Deep response to MM therapy is a biomarker for progression-free survival, suggesting association of microbial signature and patient outcome. Short chain fatty acids, mainly butyrate, produced by *E. hallii* and *F. prausnitzii*, are associated with minimal residual disease negativity at the end of induction therapy for MM.

Avet-Loiseau *et al.*^[18] searched abstracts in PubMed, The American Society of Hematology, and the European Hematology Association for *myeloma*, *minimal residual disease*, and *clinical trial*. Because of the need to evaluate the treatment effect on MRD response, only randomized studies for subjects with newly diagnosed multiple myeloma (NDMM) were included. Details on the MRD-tested populations were required. The authors conducted a meta-analysis

to evaluate MRD status as a valid progression-free survival (PFS) surrogate in patients with NDMM. The results support the claim that MRD status can be used as a surrogate for PFS in NDMM.

B-cell-intrinsic epigenetic modulation of antibody responses by dietary fiber-derived butyrate

Epigenetic modification or factors, such as histone deacetylation and microRNAs, have been shown to interact with B-cell genetic programs to shape antibody responses, while the dysfunction of epigenetic factors has been found to lead to autoantibody responses.

Sanchez *et al*^[19] demonstrated a protocol for inducing B cells to undergo class-switch DNA recombination (CSR) and plasma cell differentiation, treating these B cells with HDAC inhibitor (HDI), and analyzing miRNA and miRNA expression. The authors defined that in B cell induced to undergo CSR and plasma cell differentiation, HDI, an epigenetic regulation, selectively modulates miRNA and miRNA expression and alters CSR and plasma cell differentiation. Butyrate and propionate are metabolites from dietary fermentation by gut microbiota that affect differentiation or functions of T cells, macrophages and dendritic cells. Sanchez *et al*^[20] exhibited that at low doses butyrate and propionate directly impact B cell intrinsic functions to moderately enhance class-switch DNA recombination (CSR), while decreasing at higher doses over a broad physiological range, artificial insemination by donor and Blimp 1 expression, CSR, somatic hyper-mutation and plasma cell differentiation. By acting as HDAC inhibitors, not as energy substrates or through GPR-engagement signaling in these B cell intrinsic processes, butyrate and propionate impair intestinal and systemic T-dependent and T-independent antibody responses. Their epigenetic impact on B cells extends to inhibition of autoantibody production and autoimmunity in mouse lupus models. The findings outline an important B cell intrinsic mechanism that takes cues from environmental epigenetic modifiers, i.e., dietary fibers and related catabolites by intestinal microbiota, to regulate B cell differentiation processes critical to antibody and autoantibody responses.

CASE REPORTS

Case report 1: Multiple myeloma

Multiple myeloma (MM), an incurable malignancy of the plasma cells in the bone marrow, has a complex pathogenesis due to clonal heterogeneity. Due to heterogeneity within the cancer cell microenvironment, cancer cell populations employ a dynamic survival strategy to chemotherapeutic treatments, which frequently results in a rapid acquisition of therapy resistance. Epigenetic strategies to reverse drug resistance in heterogeneous MM were demonstrated by Issa *et al*^[21]. Clonal evolution of MM cells and the bone marrow microenvironment changes contribute to drug resistance. Targeting MM-cancer stem cells (CSCs) is clinically relevant, and different approaches have been suggested to target molecular, metabolic and epigenetic signatures, and the self-renewal signaling characteristic of MM CSC-like cells. Autologous peripheral blood stem cell transplantation (APBST) is a major advance in treatment of MM and bone marrow insufficiencies, but its use is limited by important complication. APBST uses healthy blood stem cells from the patient own body to replace the patient's diseased or damaged bone marrow. APBST is most often used to treat MM.

A 51-year-old male having weak body temperature and lack of sleep, was diagnosed MM with back bone fracture on September 2014. Then, he was administrated thalidomide and ingested aloe vera juice (AVJ). Furthermore, he started APBST therapy on September 2015. After two years-medical treatment, he was remitted without

any drug, showing normal range in blood inspection and bone density, and has a good QOL in 2019. The case report suggests how APBST therapy recovered MM and how thalidomide with adjuvant AVJ cured MM patient without any side effect.

Case report 2: Acute leukemia

A 12-year-old boy with deep fatigue, high-body temperature, decreased body-weight and loss of appetite, was diagnosed as an outpatient of acute leukemia on May 15, 2001. He was injected anticancer drug kiroside with prednisolone in 4-Kur style. On May, 2004 after the treatment of acute leukemia therapy, he had a relapse with severe body-weight loss and deep fatigue, and started again injection of anticancer therapy. He was diagnosed no medical treatment, because of occurrence of tumor lysis syndrome on May 31, 2004. He started anticancer therapy with kiroside and uromitexan, and aloe vera juice (AVJ) with bee pollen supplement. He recovered good blood examination results on July 7, 2004. Then he received radiation cancer therapy on September 10, 2004 and bone marrow transplantation treatment from his brother on September 16, 2004. During September 10 to October 4, 2004 AVJ ingestion was suspended because of immune-stimulation with AVJ and then AVJ ingestion with bee products was started again. After 50 days on hospitalization he came out the hospital and had a relapse based on myeloid examination. He had no choice to treat the myeloid leukemia. Then he decided to ingest AVJ with bee products supplementation during 5 years. On January 2020 he recovered good QOL levels at 31-year old.

Case report 3: Malignant lymphoma

A 43-year-old lady with deep helps and asthma around neck was investigated neck biopsy and diagnosed as malignant lymphoma (ML) on October 30, 2006, and hospitalized on November 1, 2006. She was examined myeloid with CT scan and found as stage 4 in follicular lymphoma. She started the RCVP treatment (rituximab, cyclophosphamide, vincristine and prednisolone) for 2 Kur for 3 weeks. She started to ingest AVJ with bee products supplementation on February 13, 2007 and remitted to the anticancer treatment. Then she was recommended to take autologous hematopoietic stem cell transplantation, and treated the transplantation on June 26, 2007. She well stabilized blood examination on July 5, 2007 and discharged from the hospital on July 11, 2007. Since then she has well QOL levels on January 31, 2020.

Clinical results in continuous intrathecal or intracavitary administration of sodium butyrate for patients with recurrent and progressive malignant glioma: Experience with 23 cases

Based on the experimental research (a total of 23 patients of glioblastoma, 19 and anaplastic astrocytoma, 4; between Oct. 2001 and Feb. 2006 and followed until Oct. 2006), continuous intrathecal or intracavitary administration of sixty milli-molar sodium butyrate for recurrent and progressive malignant glioma (MG) patients was clinically attempted by Nakagawa *et al*^[22]. The authors evaluated the clinical potential of intrathecal use of sodium butyrate for malignant glioma in experimental research. The therapy was well tolerated and resulted in long-term inhibition of the growth of the tumor in some patients and showed therapeutic safety.

DISCUSSION

Multiple myeloma (MM), acute leukemia (AL) or malignant lymphoma (ML), which is derived from immunoglobulin-producing plasma cells, was treated using novel cancer agents and autologous

peripheral blood stem cell transplantation (APBST) therapy. Although these clinical treatments have improved MM prognosis, it is still remains an incurable disease. Histone deacetylases (HDAC) are thought to have potential as next-generation therapeutics because HDAC isoform-selective inhibition is effective in MM cells. An inhibitor butyrate of HDAC, which leads to alterations of several important oncogenic signaling pathways, reduces gut inflammation by promoting T-reg differentiation with decreased activities of the NF- κ B and STAT3 pathways. Butyrate has the potential to be incorporated into cancer prevention and treatment regimens. Furthermore, in MM patients with minimal residual disease (MRD) negativity treatment response, a high abundance of the butyrate producer *E. hallii* was identified and an important B cell intrinsic mechanism that takes cues from environmental epigenetic modifiers to regulate B cell differentiation processes critical to antibody and autoantibody responses was expressed^[17]. The gut microbiome has received increased attention for the connection to various aspects of health and QOL^[23].

The case reports showed efficacy of APBST treatment, cancer therapy drugs, and adjuvant aloe vera juice (AVJ) supplementation to MM of 51-years old male patient, AL of 12-year-old boy, and ML of 43-year old lady without any side effect. Beneficial use of HDAC inhibitor butyrate may be overcome by several approaches with anti-MM agents and an adjuvant AVJ. Present studies indicate that microbiota composition such as butyrate in the gut could have implications for treatment response in MM, AL, and ML.

Native or over-acetylated or de-acetylated acemannan pre-treatment to mice has shown to reduce the γ -radiation-induced oxidative damage and hematopoietic injuries by free radical scavenging and macrophage activation (secretes pro-hematopoietic factors through TLR-4) respectively. Over-acetylated acemannan has stronger effects on immunomodulation/radioprotection. Thus acemannan acetyl group modulates immune system, while hydroxyl group participates in free radical scavenging^[24].

Stomatitis is the most common complication of chemotherapy. The study aimed to assess the effect of aloe vera solution on stomatitis and its pain intensity in patients undergoing chemotherapeutic procedures. The randomized controlled clinical trial, 64 patients with acute myeloid leukemia and acute lymphocytic leukemia undergoing chemotherapy were randomly divided into control and intervention group. The intervention group patients were asked to wash their mouths with 5 ml of aloe vera solution for two minutes three times a day for 14 days. The results showed that aloe vera solution can improve the patients' nutritional status, reduce stomatitis and its pain intensity, and increase the patients' satisfaction and QOL. Trial registration number: IRCT20140928193118N1^[25].

SUMMARY

Present case reports summarize that the patient diagnosed as severe multiple myeloma, acute leukemia or malignant lymphoma, was treated with cancer therapy and autologous hematopoietic stem cell transplantation after potentiation to normal blood levels with AVJ supplementation. The AVJ supplementation suggests that the gut microbial status in each patient was improved on side effects with cancer therapy producing for normalized blood conditions and contributes to be well QOL levels with AVJ-adjuvant activity. ACM as a promising vaccine adjuvant could ensure maintenance of homeostasis for hematologic malignancy and butyrate, one of gut metabolites of ACM, may be evaluated to clinical potential intrathecal or intracavitary use for malignant glioma.

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