第19回 日本緩和医療学会総会

CM2-2　がん診療連携拠点病院の新要件　傾向と対策

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2014年に、がん診療連携拠点病院の指定要件が大幅に変更された。新指定要件は、従来のがん診療提供体制で課題となっていた拠点病院間の格差に対応して、一定の集約化をめざす、拠点病院未設置の空白2次医療圏に対して地域がん診療病院の新設、がん診療提供体制に関するPDCAサイクルの確保などを対応案として掲げている。緩和ケアにおいても、「がんと診断されたときから身体的・精神心理的・社会的苦痛などに対して適切に緩和ケアを受け、苦痛が緩和される」ことをめざした改定が行われた。具体的には、緩和ケアチームの人員配置が強化され、専従の看護師が専門・認定看護師を配置することの義務化、都道府県がん診療連携拠点病院での緩和ケアセンターの設置が示された。主な取り組みについても、系統的スクリーニング実施の義務化、緩和ケアチーム看護師による外来看護業務の支援、対応の明確化、迅速な対応の義務化、地域連携時の症状緩和、緩和ケア研修の受講促進が示されている。少ない人数の中で、いかに効果的にチームを運用するかが問われる時代になったと言えよう。当日は、新要件を確認しつつ、拠点病院でどのような取り組みが求められるか、緩和ケアチームのベストプラクティスを考えてみたい。

研究責任者：筆頭演者自身
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会長　　朝　田　　隆

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WS2-3

認知症の緩和ケア　総合病院の精神科医が果たす役割

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わが国では2013年に高齢化率が25％を越える未曾有の超高齢化社会を迎えた。高齢者の増加とともに，認知症患者も急増し，その対応は社会的な課題となっている。その中で，欧米を中心に認知症への緩和ケアの適応が注目されつつある。

緩和ケアは悪性腫瘍だけを対象にしているわけではない。1990年以降，緩和ケアの対象はがんから後天性免疫不全症候群，神経疾患（筋萎縮性側索硬化症），救急，集中治療領域，アルツハイマー病を中心とした老年医療，心血管疾患，呼吸器疾患，腎疾患等に広がっている。現在，欧米の緩和ケアの対象の20～30％は非悪性疾患となっている。

緩和ケアのアプローチの特徴は，疾病の経過を予測することにある。あらかじめ患者がどのような体験をしうるかを予測することができれば，患者や家族の意思決定がより容易になる。今患者が生きる上で優先順位が高い課題は何かを，患者と医療者が検討することが重要である。

認知症の経過の中には，終末期に予測される重度の身体的・精神的機能障害を抱えた生活もある一方，早期には肺炎や摂食不良による栄養障害などの健康問題も起こりうる。これらの課題に対して，「生活の質の向上」を目指した取り組みが適応となる。特に身体症状の目立たない初期においては，患者個人個人の生活の質そのものとなる。認知症が進行するに連れて，身体や精神機能の維持，併存症に伴う様々な苦痛の除去も加わる。さらに，患者とその家族は具体的なニーズがあり，適切に対応される必要がある。意思決定をめぐり，患者とその家族の間をコミュニケーションを調整することも出てくる。

総合病院の精神科医は，認知症への診療のみならず，身体治療との相互作用の見積もりと調整，地域ネットワークの支援など担う活動は幅広い。特に，身体治療との調整は，総合病院でしか担えない役割である。

WS2-4

認知症高齢者の虐待問題とその支援

いらはら診療所在宅医療部
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認知症高齢者を診療する医師にとって虐待は避けては通れない問題である。高齢者虐待防止法には，身体的虐待，心理的虐待，性的虐待，介護等放棄，経済的虐待の五つが規定されている。身体的虐待は身体拘束や向精神薬等での鎮静も場合によってはその範疇に入るとされる。このほかセルフ・ネグレクトを重視する考え方がある。セルフ・ネグレクトは独立した死亡因子とされる。病院医師が，救急外来や入院患者において発見しやすいのは，身体的虐待と介護等放棄による衰弱等であろう。認知症高齢者は記銘力や判断力低下のために経済的虐待を受けやすい。しかし，経済的虐待は把握が困難なばかりでなく，わが国が制度上，世帯を単位として社会保険料徴収や生活保護を行っている関係上，告発困難な側面もある。経済的虐待を防ぐ重要な手法である後見人制度運用において精神科医の役割は大きい。通報窓口は地域包括支援センターあるいは市町村である。市町村により対応には温度差がある。通報電話番号が地域割りで数多く存在し，適切な通報番号を見つけることが困難なことがある。虐待の背景には，家族の歴史のほかに，家族介護者の疲弊，加害者の障害や疾病の問題も珍しくない。加害者が統合失調症あるいは知的障害を抱えながら介護をしている例，アルコール問題を抱える例などがある。対応において重要な点は，「加害者を援助する」視点，「家庭全体を支援する」視点である。虐待は支援者から隔絶された「孤立した家庭」で生じることも多いが，そのような例では，病院医師が，「ごくふつうに在宅医療や在宅ケアの従事者につなぐ」だけでも事態は前向きに進展することが多い。家族介護者を疲弊から救うことで虐待状況を緩和させることができることが多いが，そこにおいて精神科医による認知症高齢者の症状緩和は大きな力を発揮しうる。深刻な例では，加害者から被害者を分離するが，そこでの医療従事者の役割は大きい。

QUALITY OF LIFE

P3-0578

Loneliness Experienced During Hospital Isolation Due to a Bone Marrow Transplant: Immunological and QOL Outcomes

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BACKGROUND: Research indicates that loneliness is adversely associated with health and quality of life (QOL) in oncology populations. An interesting link exists between the immunological effects of loneliness and bone marrow transplant (BMT) recovery. Loneliness distress amplifies cortisol production, which increases circulating neutrophils and decreases lymphocyte counts (Cole, 2008). Since higher neutrophil to lymphocyte ratios (N/L) are associated with mortality in oncology patients (Chua et al., 2011), hospital loneliness may have adverse effects on BMT recovery. METHOD: Oncology/Hematology patients were identified through Mayo Clinic of Jacksonville Transplant Log and mailed a survey ±30 days of the participants' 6-month post-transplant. Forty-one participants (M_{age} = 60, SD = 10.86; 55.3% female; 84.2% Caucasian), of which 87% completed an autologous transplant, returned a finished survey. The Functional Assessment of Cancer Therapies-BMT (Cronbach's α = 0.86–0.89) was used to measure QOL and the UCLA Loneliness Scale Version 3 (Cronbach's α = 93) was used to assess general loneliness and loneliness experienced during hospitalization. Neutrophil and lymphocyte counts and other medical information were obtained through records using PowerChart. RESULTS: Loneliness experienced during the hospital stay was independently associated with difficulty managing disease symptoms (β = 0.501, $p < 0.01$) and poorer overall QOL (β = −0.452, $p < 0.01$) 6 months after a BMT. Specifically, hospital loneliness was associated with poorer social (β = −0.424, $p < 0.01$), emotional (β = −0.341, $p < 0.05$), and functional well-being (β = −0.422, p = 0.01) 6 months post-transplant. Patients reporting greater hospital loneliness had higher N/L ratios at Day 30 when compared to those reporting less loneliness, after controlling for general loneliness and Day 0 N/L ratios ($p < 0.01$). Within-subjects effects indicated that loneliness associations with elevated Day 30 N/L ratios diminished by Day 100, $F(1, 37) = 5.28$, $p < 0.03$. CONCLUSIONS: Experiencing loneliness during BMT hospitalization is independently predictive of continued problems managing symptoms and poorer QOL 6 months after the transplant. Notably, loneliness from hospital isolation also is associated with poorer immunological functioning at 30 days post-transplant, even when controlling for baseline N/L ratios and trait loneliness. Findings support empirical and theoretical predictions that the stress from loneliness impacts the immune system through the upregulation of pro-inflammatory neutrophil cells and reduction of lymphocytes (Glaser & Kiecolt-Glaser, 2005). Immune dysregulation was most evident in 30 days post-transplant, but diminished by day 100. RESEARCH IMPLICATIONS: This is the first known study to investigate loneliness in BMT populations, with implications for loneliness theory. Theoretical predictions (Hawkley & Cacioppo, 2010) that the unsafe feelings of loneliness cause stress, with immune system consequences, are supported by N/L ratios in patients who experienced higher loneliness during BMT hospitalization. Current study revealed that acute loneliness experienced during hospital-isolation is associated with immune system dysregulation 1-month following, and degraded QOL and symptom control at 6-month post-transplant. CLINICAL IMPLICATIONS: Loneliness perceptions during BMT hospitalization may be an important factor in improving immunological recovery. Isolation is necessary for the BMT procedure, but may have unintended consequences. Although causal connections cannot be determined in the current study, results indicate that healthcare providers may have an opportunity to improve BMT recovery by attending to patients' loneliness perceptions. Loneliness interventions may reduce the distressing experience of social isolation, enhancing QOL, and recovery 6-month post-transplant (Masi et al., 2011). ACKNOWLEDGEMENT OF FUNDING: None.

P3-0192

Radiotherapy and Cognitive Function in Breast Cancer Patients Treated With Conservation Therapy

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BACKGROUND: Although protracted cognitive impairment has been reported to occur after radiotherapy even when such therapy is not directed to brain areas, the mechanism remains unclear. This study investigated whether breast cancer patients exposed to local radiotherapy showed lower cognitive function mediated by higher plasma interleukin (IL)-6 levels than those unexposed. METHOD: We performed the Wechsler Memory Scale-Revised (WMS-R) and measured plasma IL-6 levels for 105 breast cancer surgical patients within 1 year after the initial therapy. The group differences in each of the indices of WMS-R were investigated between cancer patients exposed to adjuvant regional radiotherapy ($n = 51$) and those unexposed ($n = 54$) using analysis of covariance. We further investigated a mediation effect by plasma IL-6 levels on the relationship between radiotherapy and the indices of WMS-R using the bootstrapping method. RESULTS: The radiotherapy group showed significantly lower Immediate Verbal Memory Index and Delayed Recall Index ($p = 0.001$, $p = 0.008$, respectively). Radiotherapy exerted an indirect effect on the lower Delayed Recall Index of WMS-R through elevation of plasma IL-6 levels (bootstrap 95% confidence interval = −2.6626 to −0.0402). CONCLUSIONS: This study showed that breast cancer patients exposed to adjuvant regional radiotherapy in conservation therapy might have cognitive impairment even several months after their treatment. The relationship between the therapy and the cognitive impairment could be partially mediated by elevation of plasma IL-6 levels. RESEARCH IMPLICATIONS: This study suggested that even irradiation not directed to brain areas can cause prolongation of cognitive impairment for at least some months, and that some of proinflammatory cytokines may be involved in the impairment in part. Well-designed prospective studies are needed to confirm this hypothesis. CLINICAL IMPLICATIONS: This study can lead to development of new interventions and preventions for cognitive impairment suffered by cancer patients or survivors having undergone anti-cancer treatments. ACKNOWLEDGEMENT OF FUNDING: None.

P3-0298

Factors Predicting Health-Related Quality of Life of Patients With Colorectal Cancer One Year After Surgery

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BACKGROUND: Colorectal cancer has emerged as the most common cancer in Singapore. The quality of life (QoL) has become increasing important in measuring the outcomes of colorectal cancer patients and it can have an impact on a person's psychological well-being. The aim of this study was to examine the factors influencing the quality of life of patients with colorectal cancer. METHOD: This was a descriptive correlational study. In total 304 patients who had undergone more than 1 year of colorectal cancer surgery in Singapore General Hospital were recruited. Data were collected using the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30), European Organization for Research and Treatment of Cancer Colorectal Cancer Specific Quality of Life Questionnaire (EORTC QLQ-CR29) and Hospital Anxiety and Depression Scale (HADS). Descriptive statistics, independent *t*-tests, analysis of variance, Pearson product-moment correlation coefficient and multiple linear regression were used to analyse the data. RESULTS: The response rate was 98.7% with 300 patients completed the survey. Younger patients reported a significant higher level of anxiety than older patients. Patients with religion have better QoL than those with no religion. Patients who were employed, had rectal cancer and stoma had significantly more symptoms than those in other respective subgroups. Anxiety and depression were found to be significantly correlated with global health status/QoL, functional and symptom scales of both EORTC-C30 and EORTC-CR29 scales. Multiple regression analyses identified anxiety, depression, age, religion, employment status, site of tumour and stoma were the significant predictors of quality of life. CONCLUSIONS: Anxiety and depression are the most important predictors of quality of life among patients with colorectal cancer 1 year after surgery. RESEARCH IMPLICATIONS: Our findings imply a need to further explore patients' experiences of patients with colorectal cancer, especially those who are more anxious, depressed, younger, have no religion, employed and had rectal

and estrogen in a non-pulsatile manner. This causes the disruption of the endogenous hormonal feedback systems, resulting in the down-regulation of testosterone and estrogen production. The mechanism by which they can induce psychiatric symptoms is still unknown. CLINICAL IMPLICATIONS: Considering the less frequently described psychotic effects of goserelin and the alternatives available regarding tamoxifen, the first step was to withdraw tamoxifen. A relevant clinical improvement was achieved, despite no full remission after 2 months. The patient is still on follow-up. The weight gain is now being addressed by the medical team (diet, exercise, antipsychotic management). ACKNOWLEDGEMENT OF FUNDING: None.

P1-0052

Cancer Cases in Clinical Ethics Consultation

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BACKGROUND: Not only psychosocial problems but also ethical issues are found in cancer treatments. Cultural differences are reflected in many ethical cancer cases. In the University of Tokyo Hospital, the clinical ethics consultant is receiving the ethics consultation from a medical staff from September, 2009. The contents of ethics consultations requested in the cases of cancer treatments were analyzed to examine whether there was any ethical tendency peculiar to Japan. METHOD: In the all ethics consultations requested from September 1, 2009 to March 31, 2011, the consultation cases related to cancer treatments was extracted. The extracted contents of ethics consultations related to cancer treatments were examined and what kind of ethical problem would include in the cases was analyzed. RESULTS: The number of the ethics consultations related to cancer treatments was 16 among 213 consultations (7.5%) from September 1, 2009 to March 31, 2011. About contents of ethical issues, patient's decision-making was 4/16 (37.5%) cases, "cancer notification" and "patient's relatives" was 4/16 (25%) cases, respectively, "refusal treatment" was 3/16 (18.8%) cases, and "sedation," "making a will" and "decision-making in a medical team" was 1/16 (6.3%) cases, respectively (duplicated data). CONCLUSIONS: Many of ethics consultation about cancer treatments was related to "decision-making," "cancer notification" and "patient's relatives" problems. "Decision-making" is a common ethical issue of cancer treatments in both Japan and the United States. Although cancer notification is common in the United States, whether to notify or not in cancer treatments is often consulted because cancer notification has not been definitely put into practice yet in Japan. It was found that the emphasis was on the relationship of patients and families as in "cancer notification" and "decision-making" because of strong togetherness of a patient and a family in Japan. RESEARCH IMPLICATIONS: The research for how cancer treatment are received in each cultural area is needed. CLINICAL IMPLICATIONS: In Japan, clinicians should be aware of strong togetherness of a patient and a family to facillitate cancer treatment. ACKNOWLEDGEMENT OF FUNDING: None.

P1-0174

Impact of a Health Literacy and Patient-oriented Talk for Cancer Patients at the Diagnosis. Insights about to Cure or to Care

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BACKGROUND: Few studies are available on predictors of awareness of the goals of care (GOC) in cancer patients, fewer studies on strategies to improve concordance in communication between the oncologist and patient. At least 1/3 of patients have a different understanding than the doctor about the intent of chemotherapy and among these the majority is elder and did not have adequate documentation and communicative content. We tested a new tool to explore and verify these aspects. METHOD: Our clinical pathway for cancer patient has an orientation talk to chemotherapy, which takes place in the days following the discussion between oncologist and patient about diagnosis and therapeutic program. During this interview between patient+/-family members and the reference nurse+our psychologist, we administer a seven questions survey (SQS),optimized in accordance with the principles of health literacy, to investigate patient-physician agreement about GOC. The findings of the analysis of the SQS are then returned to the oncologist to test its effectiveness in improving communicative concordance. RESULTS: From the analysis of the first 40 pilot cases we don't confirm youth age and information materials as variables predictive of oncologist-patient concordance regarding GOC. Prognosis and its effects are discriminant variables. 50% of patients are non concordant: in adjuvant setting 17%, curative 33% and palliative 87%. About possibilities of concordance rescue: in adjuvant and curative settings if there are previous depressive episodes you cannot recover concordance, but, whether non-concordance is the result of inadequate communication, the doctor can recover with validate techniques. In palliative setting there isn't generally concordance rescue(variables: time, symptoms, social support and care network, attitude of self-protection of doctors, personality structure and

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第2会場 (神戸国際展示場 2号館 1階) 6/21(土) 15:45-17:15	シンポジウム37　不眠のマネジメント～ぜひ知っておきたい非薬物療法と薬物療法アップデート～
	座長　市田　泰彦　(国立がん研究センター東病院 薬剤部) 森田　幸代　(滋賀医科大学 腫瘍センター 精神医学講座)

SY37-1　緩和医療の現場における睡眠障害の原因および非薬物療法と薬物療法

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○吉内　一浩

緩和医療の現場において、睡眠障害は頻度が高い併存疾患の1つであり、先行研究によると、少なくとも一般人口の3－4倍にあたる30%程度には睡眠障害が存在すると報告されている。睡眠障害は、患者の生活の質に大きな影響を及ぼすことが知られており、その対策は重要である。がん患者の不眠の原因に関しては、環境要因に加え、身体的苦痛、治療に用いられる薬剤、精神心理的問題など、多くの要因が関与し、しばしば評価が困難となる。治療に関しては、原因が明らかであれば、原因への対処を試みるが、実際には原因が明らかでないことや、対処が困難であることが多い。その場合には、まず、非薬物療法として睡眠衛生の指導を行うことが推奨される。他の非薬物療法としては、近年、認知行動療法（cognitive behavior therapy for insomnia; CBT－I）の効果も報告されている。薬物療法に関しては、ベンゾジアゼピン系の睡眠薬が使用されることが多いが、常にせん妄を惹起するリスクを考慮する必要がある。近年、メラトニン受容体作動薬が使用可能となったが、高齢者や呼吸器疾患を合併する場合にも使用しやすいという特徴を持つ。通常の睡眠薬では効果不十分な場合には鎮静作用の強い抗うつ薬を用いることや、せん妄のリスクが高い場合には抗精神病薬を用いることも検討する必要があり、緩和医療における薬剤選択は慎重を要する。

研究責任者：筆頭演者自身
利益相反1～8：該当無し

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Rikkunshito, a ghrelin potentiator, ameliorates anorexia–cachexia syndrome

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Anorexia–cachexia syndrome develops during the advanced stages of various chronic diseases in which patients exhibit a decreased food intake, weight loss, and muscle tissue wasting. For these patients, this syndrome is a critical problem leading to an increased rate of morbidity and mortality. The present pharmacological therapies for treating anorexia–cachexia have limited effectiveness. The Japanese herbal medicine rikkunshito is often prescribed for the treatment of anorexia and upper gastrointestinal (GI) disorders. Thus, rikkunshito is expected to be beneficial for the treatment of patients with anorexia–cachexia syndrome. In this review, we summarize the effects of rikkunshito and its mechanisms of action on anorexia–cachexia. Persistent loss of appetite leads to a progressive depletion of body energy stores, which is frequently associated with cachexia. Consequently, regulating appetite and energy homeostasis is critically important for treating cachexia. Ghrelin is mainly secreted from the stomach, and it plays an important role in initiating feeding, controlling GI motility, and regulating energy expenditure. Recent clinical and basic science studies have demonstrated that the critical mechanism of rikkunshito underlies endogenous ghrelin activity. Interestingly, several components of rikkunshito target multiple gastric and central sites, and regulate the secretion, receptor sensitization, and degradation of ghrelin. Rikkunshito is effective for the treatment of anorexia, body weight loss, muscle wasting, and anxiety-related behavior. Furthermore, treatment with rikkunshito was observed to prolong survival in an animal model of cachexia. The use of a potentiator of ghrelin signaling, such as rikkunshito, may represent a novel approach for the treatment of anorexia–cachexia syndrome.

Keywords: rikkunshito, ghrelin, anorexia, cachexia, weight loss

INTRODUCTION

Anorexia–cachexia syndrome is characterized by decreased food intake, hypoalbuminemia, weight loss, and muscle tissue wasting (Tan et al., 2014). This syndrome is observed in patients with advanced stages of various chronic diseases (von Haehling and Anker, 2010), and is a cause of their increased rate of morbidity and mortality (Evans et al., 2008). The treatment of anorexia–cachexia is, therefore, critically important for improving quality of life (QOL) in patients. The onset and development of anorexia–cachexia syndrome is typically associated with an increase in pro-inflammatory cytokine levels (Plata-Salaman, 2000). Therefore, megestrol acetate (Ruiz Garcia et al., 2013) and glucocorticoids are options for the pharmacological therapy of anorexia–cachexia; however, they have limited efficacy (Nelson, 2000; Jatoi et al., 2002). Recently, ghrelin, because of its orexigenic activity, has been suggested as beneficial to treat anorexia–cachexia syndrome (Molfino et al., 2014). Ghrelin is involved in eliciting feeding, controlling gastrointestinal (GI) motility, and regulating energy expenditure and body weight. Thus, clinical trials of ghrelin analogs in cancer cachexia are ongoing (Currow and Abernethy, 2014; Pietra et al., 2014).

Kampo medicine is Japanese traditional herbal medicine standardized with respect to the quality and quantity of ingredients under the Japanese Ministry of Health, Labour, and Welfare. It has been developed through clinical and laboratory studies based on Western-adopted experiment-based approaches (Yu et al., 2006). Rikkunshito, a type of Kampo medicine, is widely prescribed as a remedy for various upper GI syndromes. The adverse drug reaction reports involve hepatobiliary disorders, pseudoaldosteronism, and myopathy. Rikkunshito is manufactured by spray-drying a hot water extract of a mixture of eight varieties of the following crude drugs: *Atractylodis lanceae rhizoma* (4.0 g), *Ginseng radix* (4.0 g), *Pinelliae tuber* (4.0 g), *Poria* (4.0 g), *Zizyphi fructus* (2.0 g), *Aurantii nobilis pericarpium* (2.0 g), *Glycyrrhizae radix* (1.0 g), and *Zingiberis rhizoma* (0.5 g). There is increasing scientific evidence supporting the clinical use of rikkunshito (Takeda et al., 2012). It has been demonstrated that rikkunshito improves anorexia and cachexia, and the improvement is mediated by promoting endogenous ghrelin activity (Suzuki et al., 2012). A better understanding of rikkunshito's mechanism of action and its active components will contribute to the development of new therapies to improve QOL and potentially to prolong survival in patients with anorexia–cachexia syndrome. The present article reviews the pharmacological effects and clinical benefits of rikkunshito in anorexia–cachexia syndrome.

CLINICAL APPLICATIONS OF RIKKUNSHITO FOR GI DISORDERS

Functional dyspepsia, which is classified as a functional GI disorder (FGID), is defined as a disease with dyspeptic symptoms, such as postprandial fullness, early satiety, and epigastric burning, and there is no evidence of a structural disease that is likely to explain the symptoms (Tack et al., 2006). Patients with functional dyspepsia exhibit gastric dysmotility, such as delayed gastric emptying (Stanghellini et al., 1996) and impaired gastric accommodation (Tack et al., 1998).

Several clinical studies have demonstrated the effectiveness of rikkunshito in the treatment of GI disorders, including anorexia and gastric dysmotility. Tatsuta and Iishi (1993) reported that the administering rikkunshito, which is named Liu-Jun-Zi-Tang in China, for 7 days accelerated gastric emptying and reduced GI symptoms in 22 patients with chronic idiopathic dyspepsia. Placebo treatment, administered to 20 patients, produced no significant effects (Tatsuta and Iishi, 1993). A large-scale comparative clinical study of 235 patients with dysmotility-like dyspepsia was conducted (Harasawa et al., 1998). Rikkunshito-treated patients ($n = 118$) were given 2.5 g of rikkunshito three times a day for 2 weeks, and placebo-treated patients ($n = 117$) were given 2.5 g of placebo, including 2.5% rikkunshito, as control. As a result, the dysmotility-like dyspepsia generalized improvement rate (DDGI) was significantly higher in the rikkunshito-treated group than in the placebo group. Moreover, rikkunshito was effective in improving anorexia in patients with severe or moderate dyspeptic symptoms. Recently, a multicenter, randomized, placebo-controlled, parallel-group trial of rikkunshito in 247 patients with functional dyspepsia was conducted (Suzuki et al., 2014). The administration of 2.5 g of rikkunshito three times a day for 8 weeks reduced dyspepsia; epigastric pain was significantly improved and postprandial fullness tended to improve compared to the placebo treatment group. There were no severe adverse events in either group.

Gastroesophageal reflux disease (GERD) is often associated with decreased upper GI motility. The therapeutic effects of rikkunshito were reported in proton pump inhibitor (PPI)-refractory patients with GERD or non-erosive reflux disease (NERD). Four-week treatment with rikkunshito (7.5 g/day) in combination with the PPI rabeprazole (RPZ) significantly decreased the frequency scale for the symptoms of GERD (FSSG score) in 104 patients with GERD, which is similar to the decrease observed in response to treatment with a double dose of RPZ (Tominaga et al., 2012). In a randomized, placebo-controlled, double-blind clinical trial for 242 patients with PPI-refractory NERD, treatment for 4 or 8 weeks with rikkunshito (7.5 g/day) improved their mental component summary (MCS) scores in the Short-Form Health Survey-8 (SF-8), which was especially more effective in patients with a low body mass index (<22). Moreover, rikkunshito significantly improved the acid-related dysmotility symptoms of FSSG in female and elderly patients (≥ 65 years; Sakata et al., 2014; Tominaga et al., 2014).

Additionally, several clinical reports have provided evidence for the therapeutic effects of rikkunshito on GI symptoms and function (Kusunoki et al., 2010; Morita et al., 2012; Gunji et al., 2013; Tokashiki et al., 2013; Uehara et al., 2013).

BASIC STUDIES OF RIKKUNSHITO ON ANOREXIA AND GI DYSFUNCTION

Physical or psychological stress can cause anorexia and functional disorders in the upper GI tract. Several basic studies of rikkunshito on stress-related anorexia in animals have been reported. Saegusa et al. (2011) constructed a stress model by transferring mice from group-housed cages to individual cages, which are novel environments for mice. The mice stressed by the novel environment exhibited a decrease in food intake 1 and 3 h after stress, which was suppressed by pre-treatment with rikkunshito (500 mg/kg, p.o.) 1 h before the stress (Saegusa et al., 2011). Various psychological factors contribute to decreased food intake among the elderly population. Nahata et al. (2013) reported that exposure of aged mice (79–80 weeks old) to a novel environment markedly decreased food intake compared with that of young mice (6 weeks old). Rikkunshito (1000 mg/kg, p.o.) administration attenuated the decrease in 24-h food intake in stressed aged mice (Nahata et al., 2013).

Urocortin 1 (UCN), a stress hormone, acts on corticotropin-releasing factor (CRF) receptors in the brain and induces anorexia. Yakabi et al. (2011) reported that rikkunshito (1000 mg/kg, p.o.) restored the reduction of food intake in rats with intracerebroventricular administration of UCN (300 pmol). Additionally, the following studies demonstrated that the alpha-2 adrenergic receptor pathway contributes to the associated reduction in food intake (Yakabi et al., 2014).

The efficacy of rikkunshito in the treatment of GI disorders was observed in patients with dysmotility-like dyspepsia (Harasawa et al., 1998). Nahata et al. (2014) also reported the effect of rikkunshito on gastric function in an acute restraint stress mouse model. Mice exposed to restraint stress for 60 min exhibited delayed gastric emptying. Gastric motility, which was wirelessly measured using a strain gage force transducer, was also decreased by restraint stress. Rikkunshito (250 mg/kg, p.o.) administration improved the restraint stress-induced delayed gastric emptying and decreased postprandial gastric contractions (Nahata et al., 2014). These findings suggest that rikkunshito ameliorates several types of stress-induced anorexia and gastric dysmotility.

RIKKUNSHITO'S MECHANISM OF ACTION

GHRELIN

Ghrelin is a 28-amino-acid peptide that is mainly secreted from the X/A-like cells in the stomach, and several tissues, including the brain, have small levels of ghrelin. It acts as a natural ligand for the growth hormone secretagogue receptor (GHS-R). Acylation of Ser-3 by the addition of *n*-octanoic acid via the polytopic membrane-bound enzyme ghrelin *O*-acyltransferase (GOAT) is essential for the biological activity of ghrelin via the GHS-R (Kojima et al., 1999; Gnanapavan et al., 2002; Yang et al., 2008).

Ghrelin plays role not only in growth hormone secretion (Kojima et al., 1999) but also in initiating feeding as an appetite stimulant (Nakazato et al., 2001). The plasma ghrelin levels increase in response to prolonged fasting and they decrease rapidly after feeding, suggesting that peripheral ghrelin is significant for appetite regulation (Cummings et al., 2001; Tschop et al., 2001). Ghrelin signals are transmitted to the *nuclei* of the solitary

tract via the vagal afferent pathway and they activate the orexigenic neuropeptides neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons in the hypothalamic arcuate nucleus (ARC), resulting in appetite stimulation (Date et al., 2002; Chen et al., 2004). Additionally, ghrelin has much broader physiologic functions (Kojima and Kangawa, 2005), including controlling GI motility (Fujino et al., 2003), regulating energy expenditure (Asakawa et al., 2001), and suppressing inflammation (Dixit et al., 2004; Granado et al., 2005).

The central or peripheral administration of ghrelin strongly stimulates food intake and increases fat mass, leading to weight gain in animals (Tschop et al., 2000; Asakawa et al., 2001; Nakazato et al., 2001). The intravenous administration of ghrelin in healthy humans increased visual analog scores for appetite and energy intake from a buffet lunch by 28% (Wren et al., 2001). These results suggest the possible clinical applications of ghrelin as a potent stimulator of appetite.

PROMOTION OF GHRELIN ACTIVITY BY RIKKUNSHITO

The inhibitory effects of rikkunshito on anorexia and gastric dysmotility are thought to be involved in promoting endogenous ghrelin activity. Takeda et al. (2008) demonstrated that rikkunshito ameliorated anorexia in rats treated with cisplatin by inhibiting the decrease of ghrelin levels in the plasma. This is the first report showing that rikkunshito stimulates ghrelin secretion in rats (Takeda et al., 2008). Selective serotonin reuptake inhibitors (SSRIs), including fenfluramine, decreased the plasma ghrelin levels and changed GI motilities in rats. The oral administration of rikkunshito to fenfluramine-treated rats increased the plasma ghrelin levels, food intake, and gastric emptying rate and improved GI dysmotility. The positive effects of rikkunshito on dyspeptic symptoms disappeared after treatment with the GHS-R antagonist (D-Lys3)-GHRP-6, suggesting it mediates the ghrelin signal (Fujitsuka et al., 2009). The ghrelin-mediated appetite-stimulatory effect of rikkunshito was also observed in novel-environment-stressed mice (Saegusa et al., 2011) and UCN-treated rats (Yakabi et al., 2011). Intra-gastric administration of rikkunshito (4 g) is reported to induce fasted phasic contractions in the duodenum and jejunum and to accelerate gastric emptying in dogs. The plasma ghrelin level 150 min after the administration of rikkunshito was significantly higher than the control value (Yanai et al., 2013). Wang et al. (2014) reported that rikkunshito enhanced the fasting plasma levels of ghrelin and alleviated the delayed gastric empty in L-dopa/carbidopa-treated naïve and Parkinson's disease rats, partially through ghrelin-related mechanisms.

Ghrelin is predominantly produced in gastric X/A-like cells and activates the orexigenic neuropeptides NPY/AgRP in the hypothalamus through the GHS-R in the vagal afferent terminal in the stomach (Date et al., 2002). Rikkunshito-treated rats exhibited elevated gene expression of gastric ghrelin and hypothalamic NPY. The afferent activity of the gastric vagus nerve decreased with the intravenous administration of ghrelin. A similar effect was observed with the intraduodenal administration of rikkunshito (1,000 mg/kg; Asakawa et al., 2001; Fujitsuka et al., 2011). Gastric ghrelin signals induced by the administration of ghrelin (10 ng, i.v.) or rikkunshito (1,000 mg/kg, i.d.) stimulated the efferent activities of both the gastric and the celiac branches of the vagus nerve, which is involved in GI motor activities (Fujino et al., 2003). These findings suggest that rikkunshito activates the ghrelin signal in the vagus nerve. Additionally, gastric vagotomy eliminated the stimulatory effect of ghrelin (10 ng, i.v.) on the efferent activities of the gastric vagus nerve but did not influence the effects of rikkunshito (1,000 mg/kg, i.d.), suggesting rikkunshito acts in part through the GHS-R in the hypothalamus.

Clinical trials have revealed a significant increase in the concentration of circulating ghrelin with rikkunshito. Matsumura et al. (2010) demonstrated that the administration of rikkunshito (7.5 g per day) for 2 weeks increased the plasma ghrelin levels in 21 healthy volunteers. Takiguchi et al. (2013) demonstrated a significant attenuation of GI symptoms after treatment with 2.5 g of rikkunshito for 4 weeks in 25 patients who had undergone gastrectomy. The mean ratio of the acyl-/total ghrelin concentration increased after rikkunshito administration (Takiguchi et al., 2013). Arai et al. (2012) conducted a parallel, randomized, controlled trial of rikkunshito or domperidone for 4 weeks for 27 patients with functional dyspepsia. Upper GI symptoms based on the Gastrointestinal Symptom Rating Scale (GSRS) score were ameliorated in both groups, but the efficacy of rikkunshito was accompanied by an increase in the ghrelin levels (Arai et al., 2012).

TARGET MOLECULES AND ACTIVE COMPONENTS OF RIKKUNSHITO

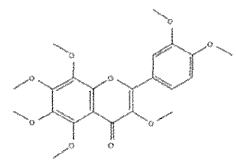
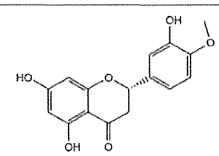
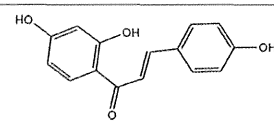
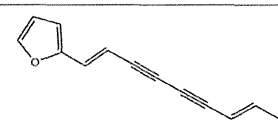
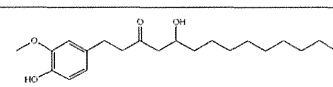
Rikkunshito was reported to regulate ghrelin secretion, ghrelin receptor sensitization, and ghrelin degradation, suggesting that rikkunshito synergistically promotes endogenous ghrelin activity (Uezono et al., 2012). As shown **Table 1**, some target molecules and active components of rikkunshito involved in these effects were identified. Summary of the rikkunshito's mechanism of action was shown **Figure 1**.

SEROTONIN 2b/2c RECEPTORS

The central serotonin (5-HT) system is implicated in the processes of meal satiation and satiety (Vickers et al., 2001, 2003; Halford et al., 2007). Takeda et al. (2008) demonstrated that 5-HT produced during treatment with cisplatin stimulates the 5-HT2b receptor in the stomach and the 5-HT2c receptor in the central nervous system, resulting in decreased plasma ghrelin. Heptamethoxyflavone, hesperetin (an aglycon form of hesperidin), and isoliquiritigenin, which are components of rikkunshito, antagonize 5-HT2b/2c receptors and stimulate ghrelin secretion in cisplatin-treated rats. Fenfluramine decreased plasma ghrelin and changed ghrelin-mediated GI motor activities through the central 5-HT2c receptor. The oral administration of hesperidin to fenfluramine-treated rats restored GI dysmotility (Fujitsuka et al., 2009). These findings suggest that these components of rikkunshito augment ghrelin secretion through antagonizing the 5-HT2b/c receptors.

Nahata et al. (2013) demonstrated that exposure of aged mice to a novel environment up-regulated hypothalamic 5-HT2c receptor mRNA expression. 5-HT2c receptor signaling enhancement and the subsequent activation of the CRF-corticosterone pathway were involved in novelty-induced hypophagia in aged

Table 1 | *Target molecules and active components of rikkunshito.*

Target molecules	Active components (Crude drug)	Structure	Reference
5-HT2b/2cR	3,3′,4′,5,6,7,8-Heptamethoxyfkvone (Aurantii nobilis pericarpium)		Takeda et al. (2008)
	Hesperetin an aglycon form of hesperidin (Aurantii nobilis pericarpium)		Takeda et al. (2008)
	Isoliquiritigenin (Glycyrrhizae radix)		Takeda et al. (2008)
GHS-R	Atractylodin (Atractylodis lanceae rhizoma)		Fujitsuka et al. (2011)
Ghrelin deacylating enzymes	10-Gingerol (Zingiberis rhizoma)		Sadakane et al. (2011)

mice. The 5-HT2c receptor antagonist SB242084 or rikkunshito administration attenuated the decrease in food intake and increased corticosterone levels in stressed aged mice (Nahata et al., 2013).

Additionally, *in vitro* studies using fura-2 microfluorometry have revealed that rikkunshito influences the effect of 5-HT on hypothalamic neurons. Administration of 10^{-5} mol/L 5-HT increased the cytosolic Ca^{2+} concentration in single neurons isolated from the paraventricular nucleus (PVN) of rats. These changes were inhibited by the administration of 100 μg/mL of rikkunshito to the PVN neurons, 83% of which subsequently demonstrated immunoreactivity to CRF (Fujitsuka et al., 2011). Administration of 5-HT increased the cytosolic Ca^{2+} concentration in ARC neurons, and 80% of the 5-HT-responsive neurons were immunoreactive to pro-opiomelanocortin (POMC). Rikkunshito and isoliquiritigenin counteracted 5-HT-induced 5-HT2c receptor-mediated Ca^{2+} signaling in POMC neurons (Arai et al., 2013). These results suggest that the inhibition of the 5-HT 2c receptor expressed on CRF neurons (Heisler et al., 2007) or POMC neurons (Heisler et al., 2003) could be responsible for rikkunshito's attenuation of anorexia.

GHRELIN RECEPTOR

Growth hormone secretagogue receptors are located in peripheral several tissues and central neurons, including NPY neurons. Ghrelin increases the cytosolic Ca^{2+} concentration in the NPY neurons of the hypothalamic ARC (Kohno et al., 2003), and this effect is linked to stimulation of appetite (Kohno et al., 2007). Compared to 10^{-12} mol/L ghrelin administration, pretreatment with rikkunshito enhanced the ghrelin-induced increase in cytosolic Ca^{2+} levels in isolated fura-2-loaded rat ARC neurons, which were subsequently shown to be NPY neurons by immunocytochemistry (Fujitsuka et al., 2011). Furthermore, Ca^{2+} imaging analysis using fluorescence of G-CAMP2 revealed that rikkunshito (100 μg/mL) had no effect on the cytosolic Ca^{2+} concentration; however, it enhanced the duration of the cytosolic Ca^{2+} concentration increased by 10^{-7} mol/L ghrelin in GHS-R-expressing COS cells. Rikkunshito also increased the binding activity of [^{125}I]-ghrelin to the GHS-R.

To identify active component of rikkunshito, the 43 compounds (100 μmol/L) contained in rikkunshito were screened. As a result, atractylodin showed a marked increase in ghrelin/GHS-R binding activity. Atractylodin also sustained the ghrelin-induced cytosolic Ca^{2+} increase in GHS-R-expressing cells (Fujitsuka et al., 2011). These results suggest that atractylodin is active component of rikkunshito, which potentiates the action of ghrelin by presumably sensitizing the ghrelin receptor.

Nahata et al. (2012) demonstrated that ghrelin increased antral motility in sham-operated rats but not in GERD rats. However, in GERD rats treated with rikkunshito, a significant increase in

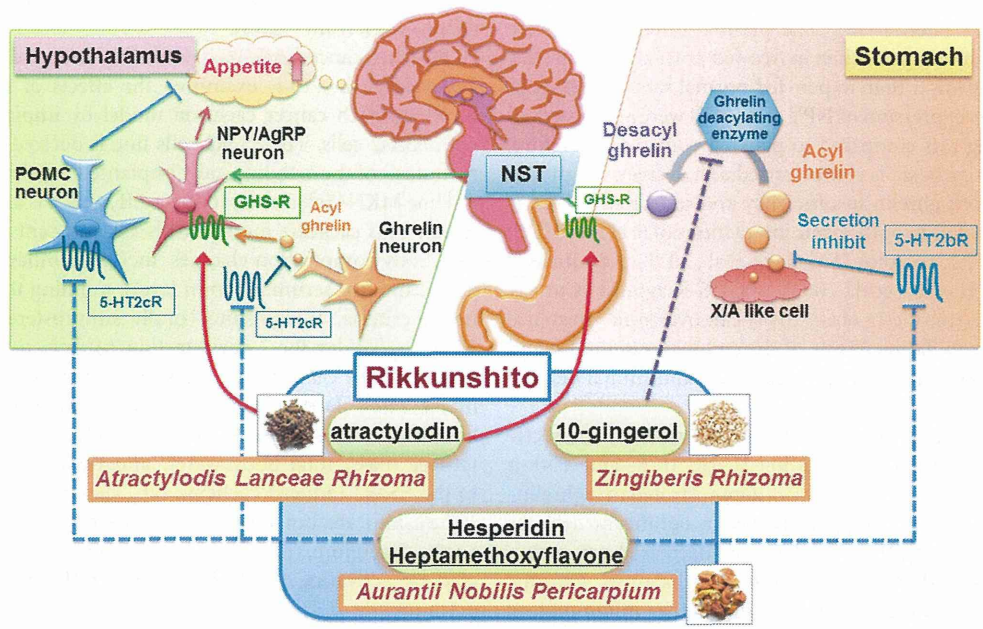


FIGURE 1 | Summary of the mechanism of action by some ingredients of rikkunshito. Rikkunshito synergistically promotes endogenous ghrelin activity. The ingredients of rikkunshito such as heptamethoxyflavone and hesperetin (an aglycon form of hesperidin), antagonize 5-HT2b/2c receptors in the stomach and the hypothalamus, which are related to ghrelin secretion. Atractylodin activates ghrelin receptors in the stomach and the hypothalamus. 10-Gingerol inhibits ghrelin deacylating enzymes in various tissues, including the stomach. The potentiation of ghrelin signaling pathways may be responsible for rikkunshito's attenuation of anorexia. POMC, pro-opiomelanocortin; GHS-R, ghrelin receptor; NST, nucleus tractus solitarii; NPY, neuropeptide Y; AgRP, agouti-related peptide.

antral motility by ghrelin was observed (Nahata et al., 2012). These findings suggest that the physiological functions of endogenous ghrelin are potentiated by rikkunshito acting on GHS-R signaling, which may be mediated by atractylodin, an active component of rikkunshito.

GHRELIN DEGRADING ENZYME

Sadakane et al. (2011) reported that rikkunshito increased the acyl- to desacyl-ghrelin (A/D) ratio in plasma from cisplatin-treated rats. Several components of rikkunshito have inhibitory activities against ghrelin deacylating enzymes. 10-gingerol, an active component of rikkunshito, inhibited exogenous ghrelin deacylation in rats. These results suggest that the increase in the plasma ghrelin level by rikkunshito is mediated, at least in part, through inhibiting the ghrelin degrading enzyme (Sadakane et al., 2011).

CACHEXIA

PATHOGENESIS OF ANOREXIA–CACHEXIA SYNDROME

Anorexia–cachexia syndrome develops during the advanced stages of various chronic diseases, such as malignant cancer, chronic heart failure, chronic kidney disease, and chronic obstructive pulmonary disease (von Haehling and Anker, 2010). This syndrome results in a decreased QOL and increased morbidity and mortality. Cachexia is diagnosed by the presence of weight loss exceeding 5% within the previous 3–12 months, anorexia, loss of skeletal muscle, and biochemical abnormalities, such as increased inflammatory markers, anemia, and hypoalbuminemia (Evans et al., 2008). In particular, anorexia is very important in the diagnosis and treatment of cachexia-associated weight loss because a persistent loss of appetite leads to a progressive depletion of body energy stores (Argiles et al., 2010).

Cytokines participate in the development and/or progression of anorexia–cachexia (Plata-Salaman, 2000). Cancer cachectic animals exhibit increased plasma levels of cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and leukemia inhibitory factor (LIF), which are either produced by cancer cells or released by the host immune system in response to the cancer (Mori et al., 1991; Inui, 2002; Ebrahimi et al., 2004; Perboni and Inui, 2006; Tisdale, 2009). These cytokines in the brain or circulation augment the release of anorexigenic hormones, including 5-HT, leptin, cholecystokinin (CCK), peptides derived from the glucagon precursor, and insulin (Shintani et al., 1993; Laviano et al., 2000). Increased 5-HT concentration in the hypothalamus is demonstrated in animals with cancer (Wang et al., 2003). Megestrol acetate and glucocorticoids are options for the pharmacological therapy of anorexia–cachexia, but they have limited effectiveness (Nelson, 2000; Jatoi et al., 2002).

ROLE OF GHRELIN ON CACHEXIA

Circulating ghrelin levels are reported to increase in underweight patients with malignancy-associated cachexia (Shimizu et al., 2003; Garcia et al., 2005) and tumor-bearing animals (Terawaki et al., 2014), suggesting a failure of the adaptive feeding

response by endogenous ghrelin (Schwartz et al., 1995; Schwartz and Seeley, 1997; Flier, 1998). The plasma ghrelin levels were higher in tumor-bearing rats than in free-fed normal rats, but they were significantly lower than in pair-fed normal rats. Decreases in the hypothalamic expression of NPY and AgRP were also observed in tumor-bearing rats compared to pair-fed controls. Therefore, cancer anorexia–cachexia is characterized as a decrease in ghrelin signaling with both ghrelin insufficiency and resistance, which is mediated by excessive hypothalamic interactions of 5-HT and CRF through the 5-HT2c receptor (Fujitsuka et al., 2011). Administration of ghrelin (Hanada et al., 2003) or GHS-R agonist (Currow and Abernethy, 2014; Pietra et al., 2014) can overcome resistance to the appetite-stimulating effects of the endogenous ghrelin and improve food intake and weight gain in human and animal subjects with cachexia.

Additionally, ghrelin inhibits the production of anorectic proinflammatory cytokines, including IL-1β, IL-6, and TNF-α (Dixit et al., 2004). DeBoer et al. (2007) demonstrated that ghrelin-treated animals with cancer cachexia have a significant increase in the expression of AgRP and NPY with decreased expression of the IL-1 receptor-I transcript in the hypothalamus. Chronic kidney disease is associated with an increase in inflammatory cytokines, resulting in cachexia with muscle loss. Ghrelin-treated nephrectomized animals had a decrease in circulating inflammatory cytokines and IL-1 receptor expression in the brainstem. Ghrelin treatment in uremia results in improved lean mass accrual, which is in part due to suppressed muscle proteolysis and possibly related to anti-inflammatory effects (Deboer et al., 2008; Suzuki et al., 2013). Ghrelin administration reduced lung inflammation, protected alveolar epithelial cells, and ameliorated lung fibrosis in a bleomycin (BLM)-induced acute lung injury model in mice (Imazu et al., 2011). The combination of orexigenic and anti-inflammatory actions suggests that ghrelin has benefits in the treatment of cachexia.

ANTI-CACHECTIC EFFECT OF RIKKUNSHITO

Increasing evidence from experimental animal models has shown that rikkunshito, which synergistically promotes endogenous ghrelin activity, ameliorates several types of cachexia. These findings suggest that rikkunshito may be more effective for ghrelin resistance such as cancer anorexia–cachexia than treatment of ghrelin or GHS-R agonists.

Rikkunshito improved anorexia, gastrointesitinal dysmotility, muscle wasting, and anxiety-related behavior in AH-130 hepatoma-bearing rats (Fujitsuka et al., 2011). The authors observed anorexia 5 days after intraperitoneal injection of tumor in rats, but the administration of rikkunshito (1000 mg/kg, p.o.) increased food intake for 6 h in tumor-bearing rats. The appetite-stimulating effect of rikkunshito was blocked by the ghrelin receptor antagonist (D-Lys3)-GHRP-6 (2 μmol/kg, i.v.), suggesting that endogenous ghrelin plays a role in rikkunshito's effects. The frequency of phase III-like contractions in the antrum and duodenum, which is fasting motor activity mediated by ghrelin signaling, decreased in tumor-bearing rats. Rikkunshito (1,000 mg/kg) gradually restored the phase III-like contractions. Additionally rikkunshito (500 mg/kg, p.o. twice daily) prolonged survival in tumor-bearing rats, and this effect was enhanced by the concomitant administration of cisplatin (CDDP; 1 mg/kg, i.p., twice a week from 6 days).

Stomach cancer patients have the highest incidence of cachexia. Terawaki et al. (2014) examined the effects of rikkunshito in a novel stomach cancer cachexia model by implanting nude rats with 85As2 cells. The 85As2 cells line is derived from peritoneal metastasis of the orthotopically implanted human stomach cancer cell line MKN45cl85 and produces LIF, which is a known cachectic factor. This cachexia model involves significant anorexia, weight loss, body composition changes, increased inflammatory marker levels, and low serum albumin levels, fulfilling the cachexia diagnostic criteria. Rikkunshito (orally administered twice daily at 1,000 mg/kg/day for 7 days starting 14 days after the implantation of 85As2 cells in rats) resulted in increased food and water intake rates. Furthermore, rikkunshito substantially alleviated body weight loss and reductions in body compositions, such as fat-free mass, total body water, and total musculature weight, in the 85As2-induced cachexia rat. The anti-cachectic effects of rikkunshito are not related to tumor regression or plasma LIF levels. Therefore, these effects of rikkunshito are likely mediated by activating the GHS-R-NPY/AgRP orexigenic signaling pathway.

Tsubouchi et al. (2014a) examined the impact of rikkunshito on BLM-induced pulmonary fibrosis in mice as a model of pulmonary cachexia. In BLM mice, the administration of rikkunshito (1000 mg/kg, p.o.) for 14 days ameliorated the decrease in body weight and food intake as well as pulmonary inflammation and fibrosis. In BLM-treated *ghrelin*$^{-/-}$ and *Ghsr*$^{-/-}$ mice, rikkunshito improved pulmonary inflammation, while failing to inhibit the BLM-associated decrease in food intake and body weight (Tsubouchi et al., 2014b). Therefore, the effects of rikkunshito on anorexia and weight loss were assumed to be mediated by ghrelin signaling.

The beneficial effect of rikkunshito on survival was also demonstrated in human patients through a retrospective analysis. Pancreatic cancer patients with ascites (stage III and IV) received gemcitabine or gemcitabine plus rikkunshito. The median survival of pancreatic cancer patients with ascites who were treated with gemcitabine was significantly prolonged by the administration of rikkunshito (Fujitsuka et al., 2011). Future, large-scale clinical trials are required to determine the efficacy and safety of rikkunshito on cancer cachexia.

CONCLUSION

Cachexia syndrome develops during the advanced stages of various chronic diseases and leads to a decreased QOL and increased rate of morbidity and mortality in patients. The Kampo medicine rikkunshito is prescribed for various upper GI syndromes, such as anorexia, and is very important in the treatment of cachexia-associated weight loss. Clinical and basic studies demonstrate that rikkunshito ameliorates anorexia and cachexia, which may be mediated by synergistically promoting endogenous ghrelin activity by several components of rikkunshito. The use of a ghrelin potentiator, such as rikkunshito, is expected to represent a novel approach for the treatment of anorexia–cachexia syndrome, which is characterized as a decrease in ghrelin signaling with both ghrelin insufficiency and resistance.

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招待講演

オピオイドの効きにくいがん性腹膜炎の痛みのメカニズム解明ならびに作用機序に基づく奏効薬の選択

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キーワード：第2期がん対策推進基本計画，がん性腹膜炎，リドカイン，骨転移動作時痛，ケタミン

本邦では平成19年“がん対策基本法”が成立し，同年基本法に基づいた“がん対策推進基本計画”が策定され本格的ながん対策が開始された。5年後の平成24年には“第2期がん対策推進基本計画”が，がん患者およびその家族の思いや意向を取り上げ，さらにその実現を目指すために計画された。新たに策定された第2期計画に基づいてがん予防から適切な検査法の開発，新規治療法の開発，そして患者の望む緩和ケア実践に至る総合的対策が以前に増して推進されている。

筆者らは国立がん研究センター研究所がん患者病態生理研究分野において，基礎医学を臨床へつなげるトランスレーショナル(橋渡し)研究を行っている。今回，“がん患者の生活の質向上のために—がんの痛み，がんのつらさを和らげるための基礎から臨床へのトランスレーショナルリサーチ—”についての当研究分野の活動の一端を紹介する。

進行がん患者の約7割はがんの痛みがもっともつらい症状であると訴える。痛みは患者のquality of life (QOL) をもっとも低下させている症状の一つであり，緩和ケアの第一の目的は“がん患者を痛みから解放すること”である。本邦でも昭和61年より世界保健機関 (WHO) による“3段階WHO方式がん疼痛治療法”に沿った適切ながん疼痛対策が行われるようになった。しかしその中で見えてくるものはWHO方式の浸透に加え，“もっと工夫できるのでは”“まだまだよい方法があるのではないか”という思いである。WHO方式がん疼痛治療法を適切に用いると，およそ85-90%の方の痛みが改善するとのデータがある。しかし裏返せばまだ10-15%のがん患者は痛みが上手に取れていないことになる。

WHO方式がん疼痛治療法に従うと，痛みの強さに応じて，非ステロイド性抗炎症薬 (NSAIDs) やアセトアミノフェンからリン酸コデインなどの弱オピオイド，そしてモルヒネなどの強オピオイドへと，症状に応じて鎮痛薬の選択が行われる。加えて“鎮痛補助薬”といわれるリドカインやケタミン，デュロキセチンといった薬物が必要に応じて用いられる[1]。WHO鎮痛方式に沿っても10-15%の患者で痛みが取れないのは，生体で痛みが引き起こされるメカニズムがかなり複雑であるということであるといえる。つまり私たちの体には，医療用麻薬 (オピオイド) が効くオピオイド受容体のほかにも，痛みを抑える機構が存在すること，さらには多くの痛みを発生させる機構が存在するということである。したがって，それらのメカニズムを解明し，その結果を臨床へ迅速にフィードバックさせることはとても重要なことである。

近年の分子生物学や遺伝子工学の進歩，また痛みに関与する細胞膜受容体やイオンチャネル，あるいは鎮痛に関するオピオイド受容体などを遺伝的に欠損させたノックアウトマウスを用いた研究により，痛みに関与する生体内タンパクや物質の研究は格段の進歩を見せた。また特定の受容体やイオンチャネルを特異的に発現させたノックインマウスの登場により痛み研究はさらに飛躍を見せた。特に生体にμ，δ，κと3種類あるオピオイド

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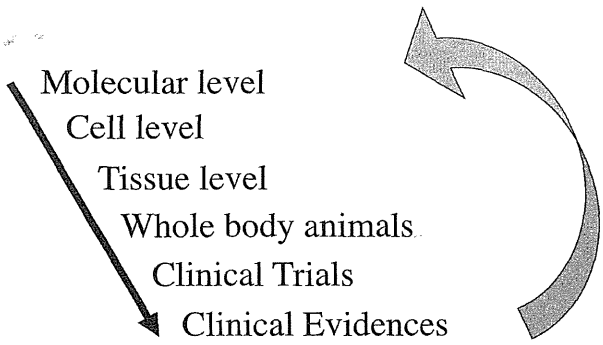


・臨床医学と基礎研究の密接な連関
・「臨床的事実」のメカニズムを普遍化
・痛みに苦しむ人に福音となる医学・研究

図 1　よりよい疼痛緩和療法の開発・実施

受容体活性化による鎮痛機構は各受容体の三次元構造も解明され[2)3)]，創薬についても分子レベルでかなり解き明かされてきた。その結果，モルヒネ，オキシコドン，フェンタニル，メサドンといった本邦で用いられているオピオイド製剤の鎮痛作用の使い分けや耐性メカニズムの違いなどが解明されてきている[3)4)]。加えて，さまざまな鎮痛補助薬がどの受容体やイオンチャネルなどを介してどのように作用しているのかという疑問についても現代科学を駆使して解明が進んでいるところである。問題は，細胞レベルや動物モデルで分かったことがヒトにもそのまま当てはまるのかということである。“細胞・動物レベルの結果のヒトへの外挿”という重要なリンクをつないでいかないと，臨床での疑問を基礎医学レベルで証明し，還元するということにはならない（図1）。加えてがん研究において重要なことは，がんモデル動物をいかに上手に作れるかということである。患者のがんの痛みを表現できる動物モデルをいかに作製するか？　モデル動物を用いて得られた結果をヒトにどのように当てはめていくか？　この溝を埋めることは重要なポイントである。

筆者らは，国立がん研究センター中央病院緩和医療科と共同で，オピオイド抵抗性腹膜播種がん性疼痛の苦痛緩和研究のため，モデル動物の作製開発を行った（図2）。図2のように“難治性疼痛研究グループ”として研究を進めた。私たちの担当は腹膜播種の腫瘍に対するリドカインの効果，ならびに脊椎骨転移に伴う動作痛に対するケタミンの効果の解析であった。がん性腹膜炎疼痛評価モデルを作製し，オピオイドの効きにくいがんの腹膜播種に伴う痛みの発現メカニズムを明らかにし，病態生理に基づいた治療薬の開発を目的とする。また，このような痛みに対して臨床現場で経験的に用いられている低用量のリドカイン全身投与の抑制効果について考察した。さらに，脊椎骨転移動作時痛評価モデルを作製し，オピオイドの効きにくい脊椎骨転移に伴う動作時痛のメカニズムを明らかにし，動作時痛に奏効するといわれているケタミンの鎮痛効果およびその作用メカニズムを明らかにするための研究を行った。

まずがん性腹膜炎モデルについて，図3に示すように，免疫不全Scidマウスに未分化型胃がん細胞である60As6Luc細胞（がん細胞自身を蛍光で光らせることができるルシフェラーゼ遺伝子を導入済み）をC.B17/Icr-scidマウスの腹腔内に移植し，臓側および壁側腹膜に腫瘍結節を形成するように胃がん腹膜播種モデルを作製した（図3）。同がん細胞移植後4週目で100％の確率でマウス腹膜に腫瘍形成が認められた。そこで移植4週後のマウスの腹部をvon Freyフィラメントを用い，疼痛評価を行った。その結果，がん移植群では機械的刺激に対して有意な疼痛スコアの増加（疼痛行動）が認められた。次に急性膵炎モデルマウスで起きる腹痛を有意に抑制することのできるモルヒネ濃度3 mg・kg^{-1}をがん移植マウスに皮下投与し疼痛評価を行ったところ，がん細胞移植マウスに疼痛行動の抑制が認められなかった（図4）。さらに高用量のモルヒネ5 mg・kg^{-1}では疼痛スコアの有意な減少が認められたものの完全な抑制を得ることはできなかった。そこでモルヒネ5 mg・kg^{-1}にリドカイン0.4 mg・kg^{-1}を併用すると，残存していた痛みがほぼ完全に抑制された（図5）。このマウスモデルでの脊髄後根神経節のμ-オピオイド受容体遺伝子ならびに痛み分子であるサブスタンスPのタンパク量を測定した。その結果，μ受容体の有意な減少とサブスタンスPペプチドの有意な増加が観察された（図6）。さらにリドカインのターゲットプロテインである電位依存性ナトリウムチャネル（Nav1.7）遺伝子発現

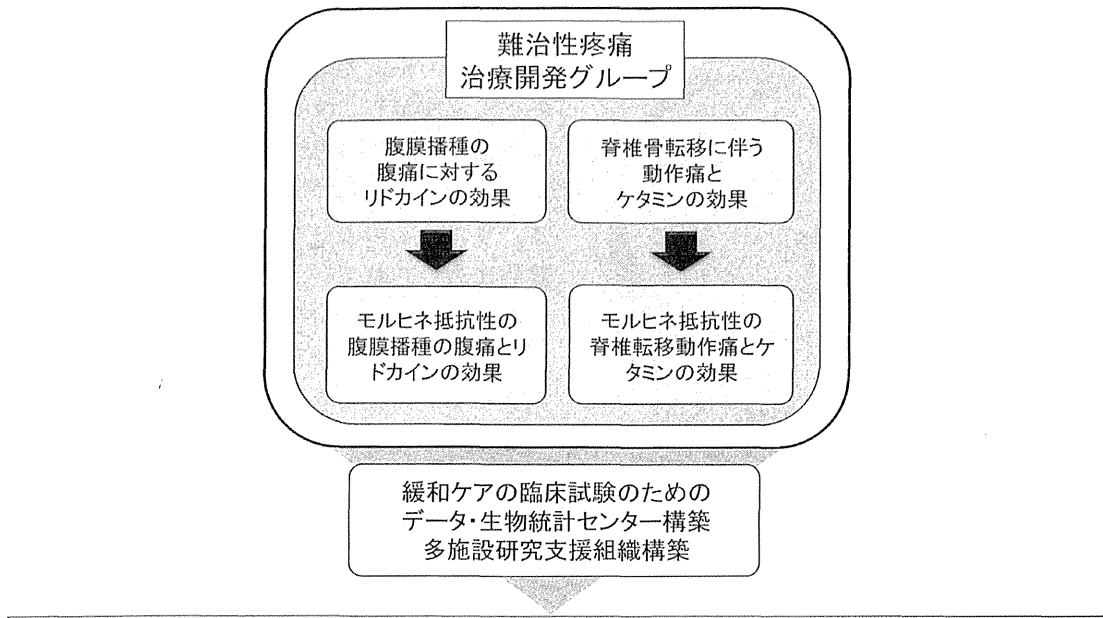


図 2　緩和治療開発プロジェクト研究推進体制

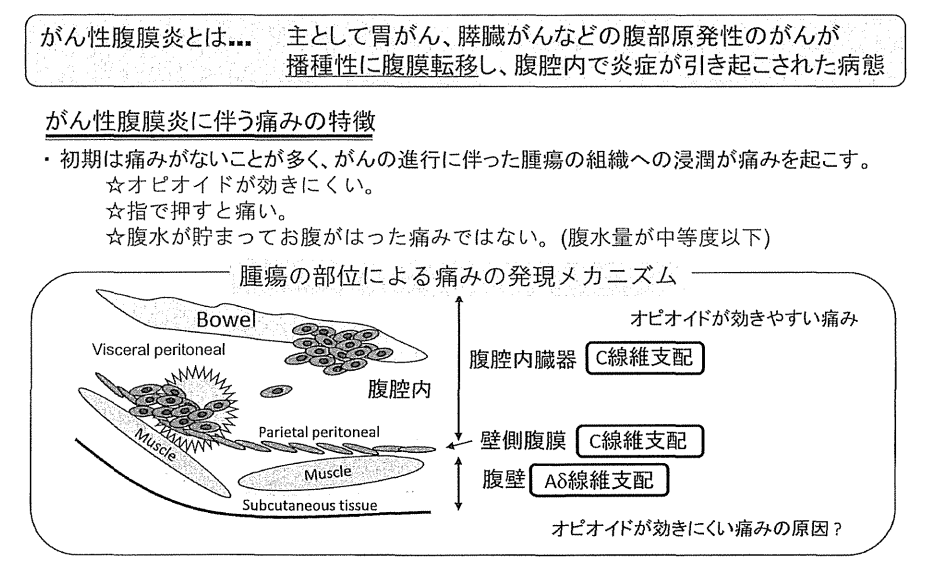
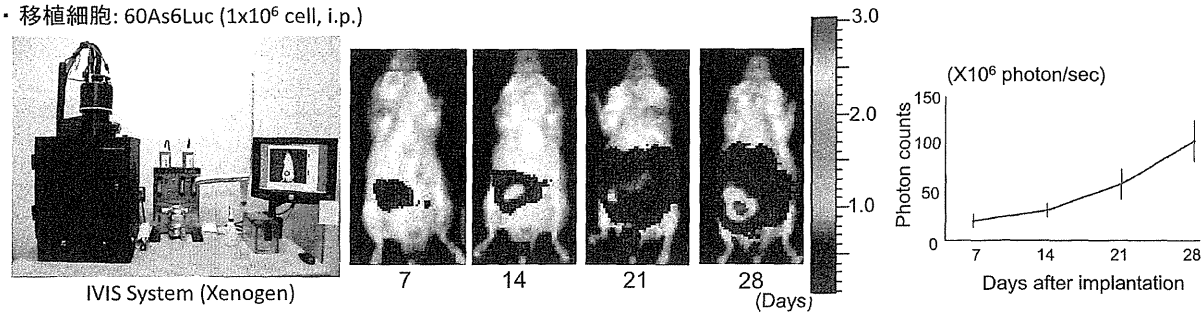


図 3　がん性腹膜炎の痛み

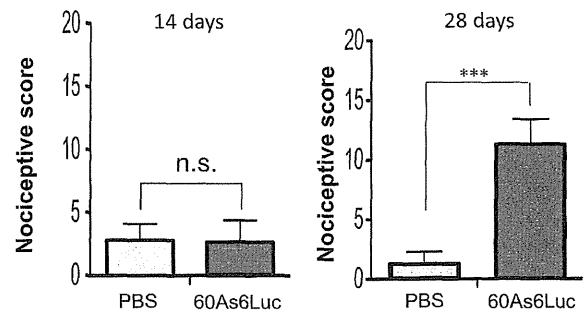
を解析したところ，オピオイド受容体の減少に加え（図 7），Nav1.7 は 30％増加していることが判明し，同モデルでモルヒネが効きにくく，リドカインが奏効する要因の一つが明らかとなった[5]。がん性腹膜炎患者の疼痛にはオピオイドが効かずリドカインの奏効する例が少なからずある。そのメカニズムは明らかになっておらず，さらに効果的なリドカイン使用，あるいはリドカインを超える臨床効果を持つ薬剤の開発などへの道は現段階では困難である。今回，リドカインの奏効するが

・使用動物: C.B17/Icr-scidマウス
・移植細胞: 60As6Luc (1x10^6 cell, i.p.)



-評価方法-(膵炎モデルと同様の方法)
0.02g のvon Frey フィラメントを用いて腹部に刺激を加えた時の逃避行動の強度を以下のスコアによって評価し、10回刺激した際の合計を nociceptive scoreとした。
(Kawabata, et al. Br J Pharmacol 2006;148:54–60)

0: 無反応
1: 素早い逃避行動
2: 強い腹部の収縮や体動



(Suzuki M,et al. Anesthesiology2012;117: 847–56)

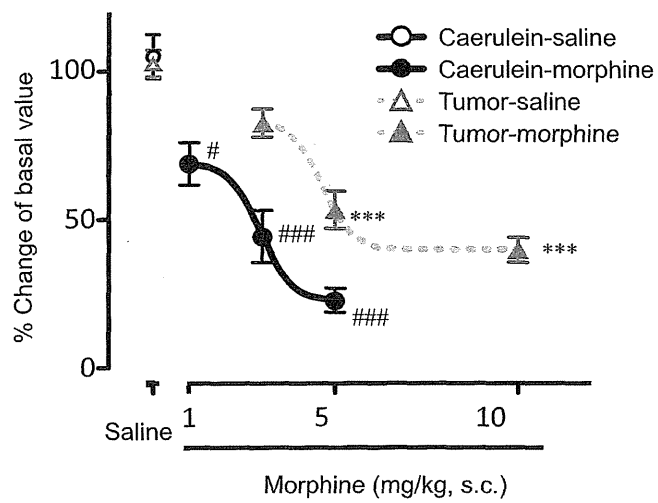
移植後 28 日目のがん移植マウスにおいて著明かつ有意な疼痛スコアの増加が出現した

図 4　腹膜播種モデルを用いた疼痛評価

<急性膵炎疼痛モデル>
コレシストキニンのアナログである caerulein を 1 時間ごとに 6 回腹腔内投与することにより作製。
→ 最終投与の 6 時間後にモルヒネ投与による評価を行った。

-評価方法-
0.02g のvon Frey フィラメントを用いて腹部に刺激を加えた時の逃避行動の強度を以下のスコアによって評価し、10回刺激した際の合計を nociceptive scoreとした。
(Kawabat, et al. Br J Pharmacol 2006;148:54–60)

0: 無反応
1: 素早い逃避行動
2: 強い腹部の収縮や体動



(Suzuki M,et al. Anesthesiology2012;117: 847–56.)

腹膜播種疼痛モデルに対するモルヒネの効果を解析したところ、急性膵炎疼痛モデルの疼痛行動をほぼ完全に抑制するモルヒネの用量では 50 % の鎮痛効果しか示さず、高用量のモルヒネを投与しても鎮痛効果の頭打ちが認められた。

図 5　腹膜播種疼痛モデルマウスに対するモルヒネの効果