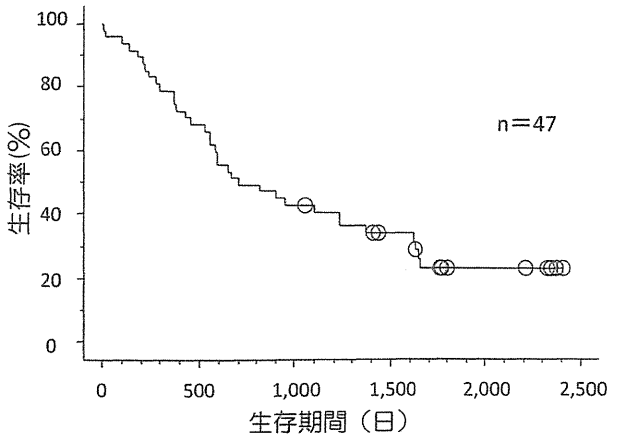

図1　CY1を唯一の非治癒因子とする胃癌に対して根治切除後のS-1単剤療法を行う第Ⅱ相試験CCOG0301[7]の長期フォローアップ成績
5年生存率が20%を超えている。

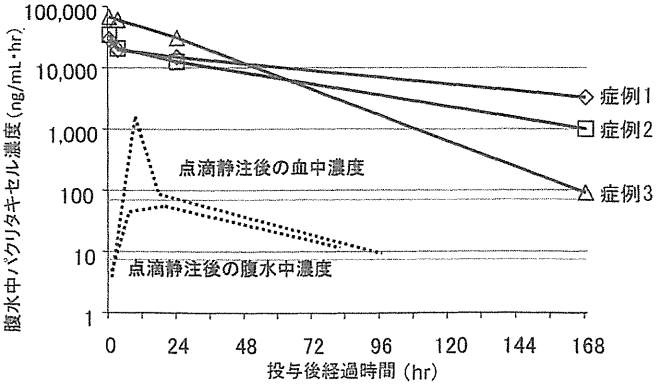

図2　腹水貯留を有する3症例にpaclitaxelを60 mg/m^{2}で腹腔内投与した場合の腹水中paclitaxel濃度の推移を実線で示す。点線で示した点滴静注後の濃度は文献13）による。

行った場合に一時的に腹腔内の濃度が上昇することは確実だが，濃度の経時的変化についてはその薬剤が腹膜表面から吸収される速度によって規定される。1990年代にはCDDPの腹腔内投与が行われたが，これは速やかに吸収されて門脈血流に入り，腹腔内の濃度が低下するとともに血中濃度が上昇するので，腹膜転移巣への効果が一時的であるのみならず，有害事象にも経静脈投与時と同様の注意が必要である。当時は規制が緩い時代であり，保険適応ではないにもかかわらず手術当日の腹腔内投与を含む術後補助化学療法群と手術単独群のランダム化比較がJCOGで行われ，漿膜浸潤を有するがR0切除が可能な胃癌に対する再発予防効果が検証された。結果として両群の生存率にまったく差が見られず，少なくとも単回投与については現在では有効な治療法とは考えられていない[14]。

一方，paclitaxelはもともと経静脈投与をした場合にも腹腔内への移行が良好で，腹水内濃度も治療域に達することが，腹膜転移に有効な理由とされている[15]。したがって，腹腔内に注入し，さらに濃度を上昇させることに意味があるかどうかは不明であるが，60 mg/m^{2}での腹腔内投与時には経静脈投与の数千倍の濃度が長期間にわたって得られており，投与1週間後でも測定が可能な域にある点は驚異的である（図2）[16]。こうなると安全性も問題となろうが，腹腔内投与後の開腹例を見る限り，タキサンの腹腔内投与では高度な炎症は惹起されないようである。卵巣癌における第Ⅰ相試験ではpaclitaxelを毎週腹腔内投与する場合の用量制限毒性は腹痛であった。推奨用量は60 mg/m^{2}と決定され[17]，その用量で行われた第Ⅱ相試験で効果と安全性が確認された[18]。ただし，腹腔内投与では腹膜表面から薬剤が浸透できる深さに限界があり[19]，腹膜表面の微小な転移や腹腔内の遊離癌細胞以外については十分な効果が上がらないことがマウスの腹膜播種モデルを用いた実験で判明している[20]。そこで全身投与との併用がポイントとなるが，その後腹膜転移を有する卵巣癌ではpaclitaxelの経静脈・腹腔内投与とCDDPの腹腔内投与を組み合わせた併用療法がpaclitaxel/CDDPの経静脈投与のみによる併用療法に勝ることが第Ⅲ相試験で示された[21]ことから，腹腔内投与が重要な役割を担うこととなった。同様の成績が胃癌でも期待されるところである。

こうした事情もあり，タキサンの腹腔内投与は胃癌の実地臨床の中でもpilot的に行われ，末期癌における難治な腹水を制御する効果を示す他，様々な状況下で使用され，有用と評価されてきた[22]。しかし，前向きの臨床試験による開発が開始される前に保険適応ではないことによる規制が厳しくなり，さらなる研究の道が閉ざされて久しい。例外として石神らの研究がある。これは既に第Ⅱ相試験までなされているS-1とpaclitaxel経静脈投与の併用療法にさらにpaclitaxel腹腔内投与を追加するものであり，第Ⅰ相試験で腹腔内投与の用量を20 mg/m^{2}とし[23]，第Ⅱ相試験では旧規約でP3の症例を多数含む胃癌腹膜転移例で78%の1年生存率を示した[24]。石神らはその後も校費負担で症例を重ね，良好な治療成績を維持しているが，このたび，高度医療評価制度を用いて腹膜転移を有する胃癌に対するS-1/CDDPを標準治療群としたランダム化第Ⅲ相試験を展開することとなった。この制度によればpaclitaxelの腹腔内投与を研究費や自費で負担し，その他の医療を保険適応とすることが可能となるが，実施に至るまでには厚労省での詳細な審査が必要であった。しかし，このランダム化試験では石神らの治療法が現在の標準治療に勝ることが示される可能性があるが，paclitaxel腹腔内投与はこの治療法に限定せず様々な局面で使用するとともに，さらなる併用療

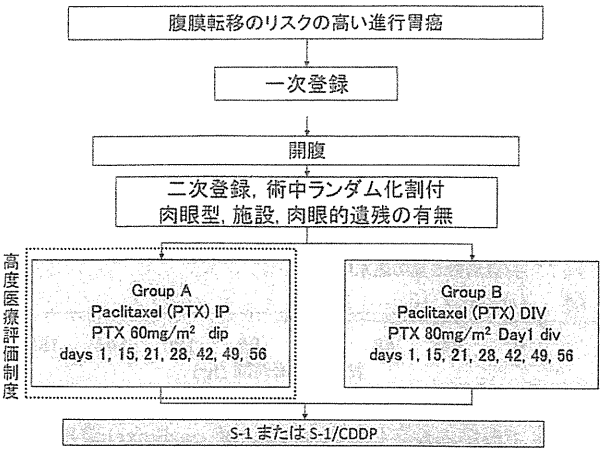

図 3 paclitaxel の腹腔内投与を検証するランダム化第Ⅱ相試験 INPACT study のシェーマ[25]。保険適応ではない腹腔内投与は高度医療として行う（文献 25）より一部改変）。

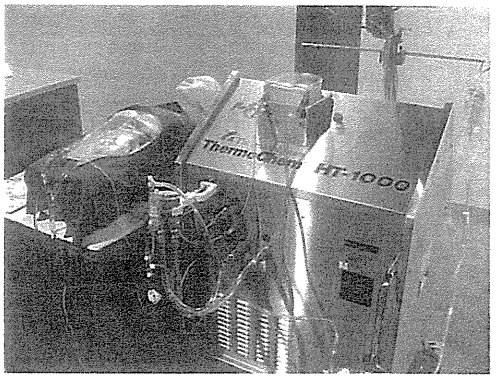

図 4 腹腔内温熱化学療法（HIPEC）に用いる環流装置。欧米の学会では普通に企業展示されており，腹膜転移を専門的に扱う医療機関では実地臨床として使用されている。

法の開発が可能となることも望まれる。そこで，筆者らは CY1 や P1 で原発巣を切除した症例（debulking surgery を受けた症例）を対象とし，術当日を含め術後 7 回の paclitaxel 腹腔内投与または paclitaxel 経静脈投与を実施した後に S-1 ないしは S-1/CDDP 療法に移行するランダム化第Ⅱ相試験を行い，腹腔内投与と経静脈投与の直接的な比較を行うこととし，参加施設を募集している（図 3）[25]。この研究も高度医療評価制度によるものであり，市中病院を含む幅広い病院が参加可能である。

これ以外に，ヨーロッパでは免疫学的機序を併せ持つ腹腔内投与専用の分子標的治療薬 catumaxomab が開発され，癌性腹水の制御に役立っていることを付記する[26]。

4．腹腔内の温熱化学療法

温熱に抗癌作用があることは広く知られており，腹膜転移については腹腔内を抗癌剤を含む温生食で還流させる試みがなされてきた。そのための機器は市販されており，欧米の学会の企業展示でも見ることができる（図 4）。これは古くは chemo-hyperthermic peritoneal perfusion（CHPP）と称されたが，現在では hyperthermic intraperitoneal chemotherapy（HIPEC）と呼ばれるのが一般的である。しかし，温熱により腹膜表面から薬剤が浸透する距離に向上が見られるとされるが，それでも肉眼的な転移巣が多数残っている状況では効果に限界があることが知られている。そこで，徹底的に転移巣を取りきる手術を行うことで，常識的には R2 切除となるものを強引に R0～R1 手術にしてしまう試みとして total peritonectomy が行われるようになった[27]。これは腫瘍量を減らす debulking surgery のコンセプトとはまったく異なる手術で，cytoreductive surgery と称されるものである。しかし，この対象に肉眼的切除のみでは治癒は望めないので，これに加えて HIPEC を行うことで効果を徹底させることになる。cytoreductive surgery と HIPEC の組み合わせは特殊な治療であるが，腹膜中皮腫などこれ以外に治療の手段がない疾患もあり，こうした稀な疾患が集積する欧米の専門施設ではこのような疾患で蓄積された経験や知見を一般の消化管癌の腹膜転移にも応用し，検証を試みている。単施設で長期間を要して集積された症例の retrospective な報告が多いが，総じて患者の PS が良好で，病巣が腹腔内に限局していることが適格条件となり，かつ結果的に R0～R1 切除が得られないと長期生存は得られていない[27]。しかし，最近になって特に大腸癌の腹膜転移例で良好な成績が報告されはじめた[28]。保険適応がない医療行為が事実上不可能なわが国では，前述のごとく，腹腔内投与の開発ですら大変な努力を要しているところであり，温熱環流装置を使用する HIPEC の開発は一層困難であろう。しかし，今後とも，新薬の開発治験に並行して，このような治療法にも目を向ける必要があるかもしれない。

まとめ

腹膜播種陽性胃癌に対する現在の標準治療は S-1/CDDP 療法である。当面は paclitaxel の腹腔内投与を含む化学療法のエビデンスを得ることに尽力するが，ゆくゆくは HIPEC の検証も視野に入れつつ，新規薬剤の登場を待ちたい。

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Plasma Diamine Oxidase Activity Is a Useful Biomarker for Evaluating Gastrointestinal Tract Toxicities during Chemotherapy with Oral Fluorouracil Anti-Cancer Drugs in Patients with Gastric Cancer

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Key Words
Diamine oxidase activity · Gastric cancer · Chemotherapy · Quality of life · Gastrointestinal tract toxicity

Abstract
Objectives: Diamine oxidase (DAO) is an enzyme that catalyzes oxidation and is highly active in the mature upper villus cells of the intestinal mucosa. This study sought to evaluate plasma DAO activities during adjuvant chemotherapy in patients with gastric cancer. ***Methods:*** We investigated 20 patients with gastric cancer who were treated with oral fluorouracil anti-cancer drugs as adjuvant chemotherapy. Plasma DAO activity was measured in all patients before chemotherapy and at 2, 4 and 6 weeks after the start of chemotherapy, and quality of life was evaluated simultaneously. ***Results:*** The median DAO activity after 4 weeks of chemotherapy was significantly decreased compared to the pre-chemotherapy levels (6.6 vs. 7.5 U/l; p = 0.038). The changes in the rate of DAO activity at 2 and 6 weeks following the start of chemotherapy in patients with gastrointestinal tract toxicity were significantly lower than in those without toxicity (p = 0.021 and 0.047, respectively). The patient cohort showed a slightly positive correlation between DAO activity and global health status and a negative correlation between DAO activity and appetite loss. ***Conclusions:*** Plasma DAO activities may be useful for monitoring and evaluating gastrointestinal tract toxicities induced by adjuvant chemotherapy with oral fluorouracil in patients with gastric cancer.

Introduction

Gastric cancer is the fourth most common cancer worldwide and is a leading cause of cancer-related death [1]. Results from a recent large-scale randomized controlled trial indicated that S-1, an oral fluoropyrimidine, is an effective adjuvant treatment for patients who have undergone a D2 dissection for locally advanced gastric cancer [2]. Consequently, using S-1 in adjuvant chemotherapy is now standard clinical practice for stage II/III gastric cancer patients in Japan. Adverse events caused by S-1 include gastrointestinal tract toxicities

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such as anorexia, nausea, diarrhea and stomatitis, which can negatively affect the nutritional status by decreasing food intake and result in disturbance or even discontinuation of chemotherapy. Therefore, preventing such gastrointestinal toxicities during chemotherapy is extremely important for improving the prognosis of cancer patients.

Diamine oxidase (DAO) is an enzyme that catalyzes oxidation, including the oxidative deamination of several polyamines, which are essential factors in cell proliferation. Therefore, DAO is an important regulator in rapidly proliferating tissues such as bone marrow and intestinal mucosa [3, 4]. In humans and rodents, DAO is found in various tissues, with small intestinal mucosa showing the highest enzymatic activity [5]. Furthermore, plasma DAO activity increases in parallel with DAO activity in the villi of the small intestinal mucosa in maturing rats [6, 7] and correlates with the severity of small intestinal mucosal lesions induced by anti-cancer drugs [8]. In addition, serum levels of DAO activities seem to be a reliable indicator of intestinal mucosal integrity and reflect quantitative changes in the small bowel mucosal mass [6, 9, 10].

Despite the common use of adjuvant chemotherapy after curative surgery for gastric cancer, the association between predictive indicators and gastrointestinal toxicities or quality of life (QOL) scores in patients undergoing chemotherapy has not been investigated. The present study measured DAO activity to evaluate mucosal injury in patients with gastric cancer undergoing postsurgical adjuvant chemotherapy. To the best of our knowledge, this is the first examination of DAO activities associated with gastrointestinal toxicities caused by chemotherapy and patient QOL.

Patients and Methods

Twenty patients with stage II or III gastric cancer, treated with oral fluorouracil anti-cancer drugs as adjuvant chemotherapy after curative operation at the Department of Surgery, Kochi Medical School (Nankoku, Japan) in 2010, were enrolled in this study. The hospital ethics committee approved the protocol and written informed consent was obtained from each patient. All patients received 80 mg of S-1 per square meter of body surface area per day, for 4 weeks, followed by 2 weeks of no chemotherapy. The plasma DAO activity was measured before chemotherapy and at 2, 4 and 6 weeks after the beginning of treatment. Simultaneously, QOL was evaluated using the European Organization of Research and Treatment of Cancer QOL Questionnaire (EORTC QLQ-C30) [11].

Measurement of Plasma DAO Activity

Blood samples were anticoagulated with heparin and centrifuged to obtain plasma for the determination of DAO activities, which was carried out according to the method of Takagi et al. [12]. Briefly, plasma was added to a cadaverine solution and incubated. The incubation mixture was then mixed with a color reagent containing DA-67 and peroxidase. After a given period, the absorption of the reaction product was measured colorimetrically at 668 nm against the blank solution using a spectrophotometer. The plasma DAO activity was expressed as units per liter.

Assessment of QOL

We assessed the QOL during chemotherapy by administering the EORTC QLQ-C30 [11]. The EORTC QLQ is an integrated system for assessing health-related QOL in cancer patients participating in international clinical trials. The QLQ-C30 contains scales and items addressing functional aspects of QOL and symptoms that commonly occur in patients with cancer. These include five functional scales, three symptom scales, a global health status scale, and six single items. All of the scales and single-item measures range in score from 0 to 100, with a high-scale score representing a higher response level. Thus, a high score for a functional scale represents a high or healthy level of functioning, and a high global health status score represents a high QOL, but a high score for a symptom scale or item represents a high level of symptomatology or problems. Kobayashi et al. [13] confirmed the validity and reliability of the Japanese version of the EORTC QLQ-C30 in Japanese cancer patients. The EORTC QLQ-C30 questionnaire was delivered to the patients during the plasma DAO activity measurements.

Statistical Analysis

Significances of difference between mean values were assessed by the two-tailed Mann-Whitney U test or the two-tailed Welch t test. The χ^2 test was used to evaluate differences between qualitative variables. Correlation between DAO activity and QOL scores using EORTC QLQ-C30 was evaluated by calculating Pearson's product moment correlation coefficient. All data are presented as the mean ± standard deviation. p values <0.05 were considered to indicate statistical significance. Statistical analysis was performed with SPSS® for Windows version 13.0 (SPSS, Chicago, Ill., USA).

Results

Patient Characteristics

Table 1 summarizes the clinical characteristics of all patients (n = 20) in this study. Our cohort comprised 16 men and 4 women with a median age of 67 years (range 44–78). The patients underwent distal gastrectomy in 13 and total gastrectomy in 7 cases and included 4 cases in stage IIA, 3 cases in stage IIB, 5 cases in stage IIIA, 4 cases in stage IIIB, and 4 cases in stage IIIC classified according to the International Union against Cancer TNM classification [14] and the TNM Supplement [15]. Six patients

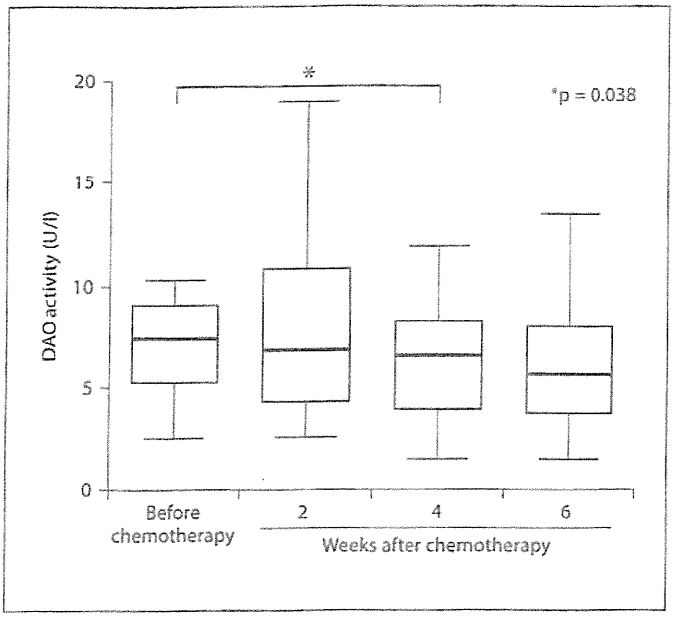

Fig. 1. Changes in DAO activities during chemotherapy. DAO activity at 4 weeks after the beginning of the chemotherapy was significantly decreased compared to the measured activity before chemotherapy.

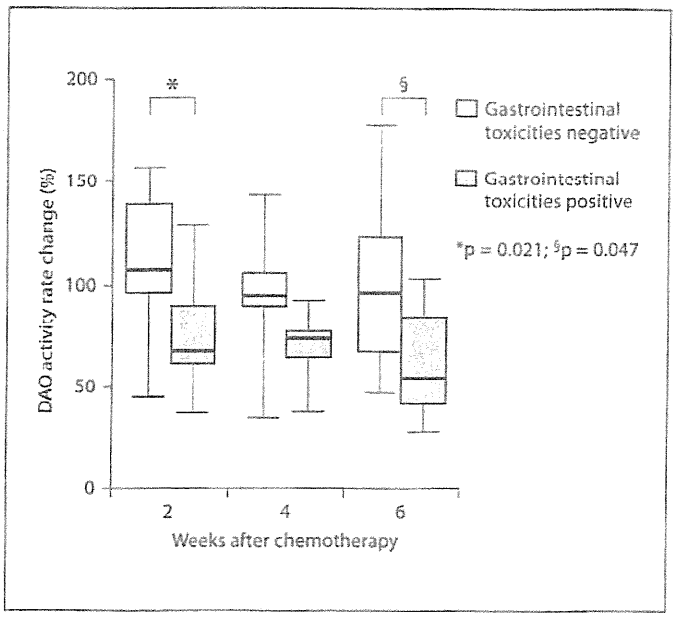

Fig. 2. Changes in DAO activities during chemotherapy relative to gastrointestinal toxicities. Changing rates of DAO activity at 2 and 6 weeks after the beginning of the chemotherapy in patients with gastrointestinal tract toxicity were significantly lower than in those patients without toxicity.

Table 1. Patient characteristics

Median age (range), years		67 (44–78)
Gender	Male	16
	Female	4
Operation method	Distal gastrectomy	13
	Total gastrectomy	7
Stage	IIA	4
	IIB	3
	IIIA	5
	IIIB	4
	IIIC	4
Gastrointestinal tract toxicities	Stomatitis	1
	Appetite loss	3
	Nausea	3
	Diarrhea	3

had adverse events related to gastrointestinal toxicities of grade 1 or 2 (defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) including stomatitis, appetite loss, nausea and diarrhea.

DAO Activities during Chemotherapy

The median DAO activity before chemotherapy and at 2, 4 and 6 weeks after chemotherapy was 7.5 (range 2.5–23.9), 6.9 (range 2.5–30.8), 6.6 (range 1.5–18.0) and 5.7 U/l (range 1.5–24.6), respectively. DAO activity at 4 weeks after the start of chemotherapy was significantly decreased compared to the levels measured before chemotherapy ($p = 0.038$; fig. 1). DAO activity at 6 weeks after the beginning of chemotherapy was decreased compared to the pre-chemotherapy level, while there was no significant difference.

Changes in DAO activities during chemotherapy relative to gastrointestinal toxicities are shown in figure 2. When DAO activities were expressed as a percentage of the level before chemotherapy to compare DAO changes among patients, the median percentage of activity rate change at 2 and 6 weeks after the beginning of chemotherapy was significantly lower in patients with gastrointestinal tract toxicity than in those without toxicity (67 vs. 107%, $p = 0.021$; 55 vs. 97%, $p = 0.047$, respectively). There were no significant differences in patient characteristics including gender, operation method and disease staging between the gastrointestinal toxicity-negative and -positive groups.

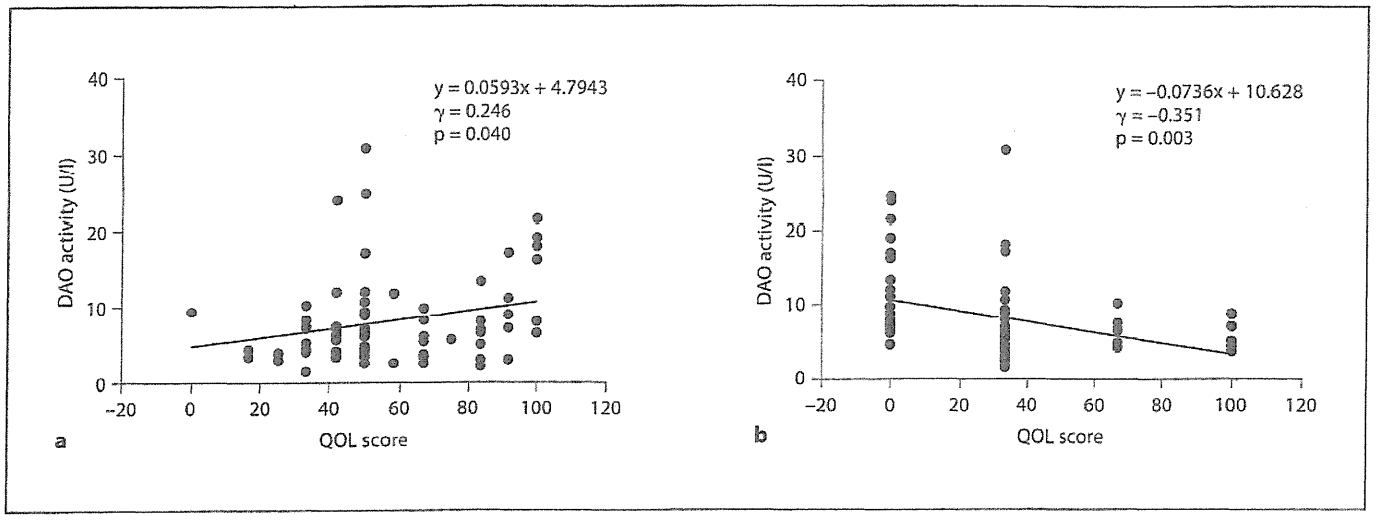

Fig. 3. Scatter plot of DAO activities and QOL scores indicative of global health status (a) and appetite loss (b). a Graph showing a slightly positive correlation between DAO activity and global health status. b Graph showing a negative correlation between DAO activity and appetite loss.

Correlation between DAO Activities and QOL

Figure 3 indicates the correlation between DAO activities and QOL based on the EORTC QLQ-C30 scores. DAO activities showed a significant positive correlation with global health status ($\gamma = 0.246$). On the other hand, there was a slight, but significant, negative correlation between DAO activities and appetite loss ($\gamma = -0.351$). There were no significant correlations between DAO activities and other domains of the QOL scores including functional scales and symptom scales.

Discussion

Our study demonstrated that plasma DAO activities were significantly decreased by adjuvant chemotherapy using S-1 in patients with gastric cancer who had undergone curative surgery. Furthermore, the findings indicated lower rates of change in DAO activity in those patients also showing gastrointestinal tract toxicity induced by chemotherapy.

A study in rats showed decreased plasma DAO activity in animals administered an oral fluorouracil anticancer drug and a correlation between the changes in plasma DAO activity and the severity of histopathological findings in the jejunal mucosa and mucosal area induced by the anti-cancer agent [16]. These results suggested that mucosal injury could be caused by a decreased release of intestinal mucosal DAO into the systemic circulation. Our report of plasma DAO activities in human patients given oral fluorouracil anti-cancer drugs for gastric cancer is the first to mirror the findings in animals.

In the present study, plasma DAO activities correlated slightly with some QOL scores, namely global health status and appetite loss. Abdominal symptoms including diarrhea and appetite loss are common gastrointestinal tract toxicities induced by cancer treatment and are caused by intestinal mucosal dysfunction due to the chemotherapeutic drugs. Diarrhea and appetite loss are the most frequent adverse events in adjuvant chemotherapy for gastric cancer, with an incidence of 59.8–61.1% [2]. Our study revealed a correlation between the severity of gastrointestinal tract toxicity due to anti-cancer drugs and plasma DAO activity in patients on chemotherapy. In patients with hematological malignancies, plasma DAO activity was significantly correlated with the severity of small intestinal mucosal lesions induced by anti-cancer drugs [8]. From the standpoint of both gastrointestinal tract toxicities and QOL, plasma DAO activity may be a useful indicator of mucosal injury following chemotherapy.

It has been reported that treatment with irinotecan hydrochloride (CPT-11), a topoisomerase I inhibitor highly effective for various cancers, caused severe diarrhea and simultaneously decreased mucosal DAO activity [17]. However, to the best of our knowledge, there is no study demonstrating a relationship between plasma DAO ac-

tivity and diarrhea, including our study. When intestinal mucosa cells became necrotic and are shed into the intestinal lumen under conditions of diarrhea, the intestinal mucosal villi decrease. This could be the case because injury of the small intestine leads to reduced DAO activity in the mucosal villi, increasing the likelihood that plasma DAO activity will decrease. Further studies are needed to elucidate whether plasma DAO activity reflects diarrhea caused by anti-cancer drugs directly.

Gastrointestinal tract symptoms induced by anti-cancer drugs are difficult to evaluate quantitatively. Previous studies have shown that glutamine, a semi-essential amino acid used as a special nutrient by intestinal mucosal cells, may protect against intestinal barrier dysfunction [18, 19]. Glutamine is also known to reduce intestinal permeability increased by stress, such as surgery and severe trauma [20]. In addition, medium-chain triglycerides enhance cell proliferation in the intestinal epithelium and mucous secretion from goblet cells in the small intestine of rat, both of which may improve mucosal injury [21]. Gastrointestinal tract toxicity was clarified by measuring plasma DAO activity, which may be one of the important quantitative biomarkers to evaluate preventive effectiveness of glutamine or medium-chain triglycerides against the gastrointestinal mucosal disorder caused by anti-cancer drugs. Furthermore, since DAO activity decreases before the manifestation of gastrointestinal tract toxicities, measuring such activity could serve as a predictive indicator of adverse events due to anti-cancer drugs and of chemotherapy tolerability.

We recognize the following limitations of the present study. First, the sample size was insufficient to clarify definitive and long-term changes in DAO activities with chemotherapy. Another limitation is that the correlation between DAO activities and QOL scores was only slight. Further studies are needed to examine the reliability and accuracy regarding the usefulness of plasma DAO activities during chemotherapy. In the future, biomarkers must be developed for estimating manifestations of adverse events or chemosensitivity with the view to selecting patient-appropriate anti-cancer drugs and improving therapeutic outcomes for all patients.

In conclusion, our study confirmed that DAO activities decrease during chemotherapy in patients being administered S-1 as adjuvant treatment after curative resection for gastric cancer. It also showed that these enzyme activity rates were lower by S-1 chemotherapy in patients with gastrointestinal toxicity than in those without toxicity. Furthermore, the level of DAO activities was slightly correlated with QOL scores including global health status and appetite loss. These findings suggested that measuring DAO activity in gastric cancer patients could be useful not only as an indicator of mucosal injury but also for the evaluation of coinciding gastrointestinal tract toxicities induced by the anti-cancer drug.

Disclosure Statement

The authors declare no conflict of interest.

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症　例

腹腔内に発生したEwing肉腫/peripheral primitive neuroectodermal tumorの2例

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Ewing肉腫（以下，ES）と末梢性未分化神経外胚葉性腫瘍（peripheral primitive neuroectodermal tumor，以下，pPNET）は主に小児から若年者にみられる骨原発の悪性腫瘍であり，まれに軟部組織からの発生も報告されている．従来，ESとpPNETは形態学的な類似点を指摘されながら，別々の腫瘍として扱われていた．2002年の新WHO分類において，両者は種々の程度に神経外胚葉への分化を示す円形細胞からなる同一の腫瘍として定義され，ES/pPNETとして1項目に分類された．軟部組織から発生したES/pPNETの発生部位の多くは傍脊柱領域，四肢，胸腔内である．今回，われわれは腹腔内に発生したES/pPNETの2例を経験した．本邦での報告は，医学中央雑誌で検索した限りでは，自験例を含め12例と極めてまれであり文献的考察を加え報告する．

索引用語：Ewing肉腫，pPNET，腹腔内腫瘍

緒　言

Ewing肉腫（以下，ES）/pPNET（Ewing sarcoma / peripheral primitive neuroectodermal tumor，以下ES/pPNET）は主に小児から若年者にみられる骨原発の悪性腫瘍であり，まれに軟部組織に発生することが報告されている．軟部組織から発生したES/pPNETの多くは，傍脊柱領域，四肢，胸腔からの発生であり，腹腔内に発生したES/pPNETは極めてまれである．今回われわれは腹腔内発生に発生したES/pPNETの2例を経験したので文献的考察を加え報告する．

症　例

症例1：78歳，女性．

主訴：腹痛．

既往歴：胆嚢結石症．

現病歴：2010年1月，腹痛を主訴に近医受診．血液検査で貧血の進行を認め，腹部CT検査で大網血腫あるいは小腸間膜の動脈瘤破裂等の腹腔内血腫と診断され経過観察されていた．2010年3月の腹部CT検査で腫瘤の増大傾向，CA125の上昇を認め，GIST等の悪性腫瘍が疑われ精査加療目的に当科紹介となった．

身体所見：特記すべきことなし．

血液所見：Hb：9.9g/dlと軽度低下を認め，CA125：194U/ml（<35U/ml）と上昇していた．

腹部CT検査：左下腹部に径13cmの内部不均一で，一部にHigh density lesionが存在する境界明瞭な腫瘍を認めた（**Fig. 1**）．

小腸造影検査：異常所見を認めなかった．以上より，腸管あるいは腸間膜原発のGISTを疑い手術を施行した．

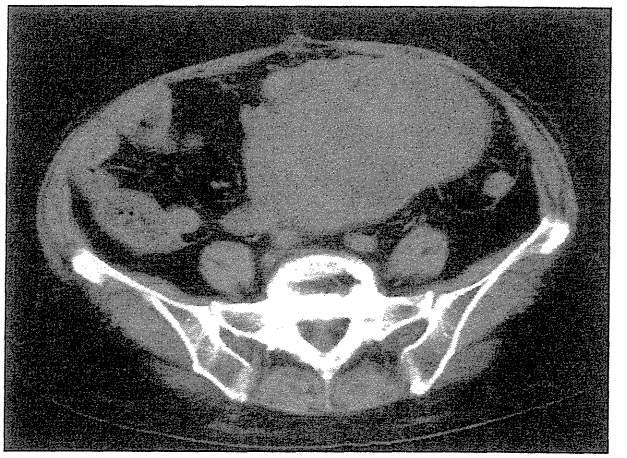

Fig. 1. Abdominal CT scan shows a large tumor.

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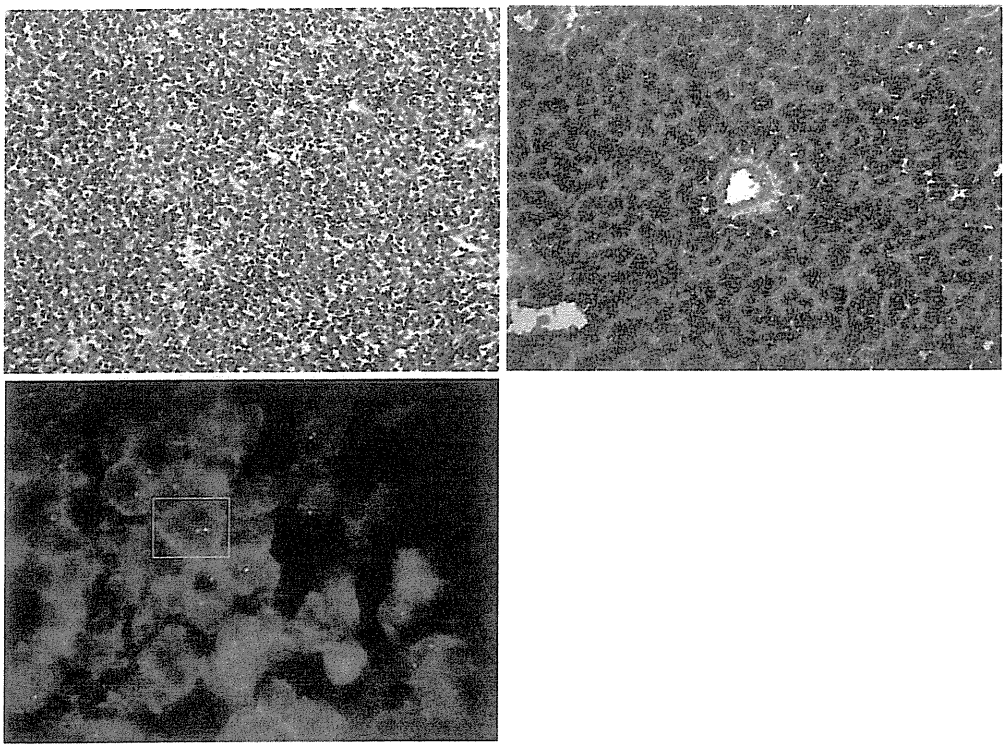

Fig. 2A. The tumor portion was composed of small round cells (H.E. ×100).
B. Immunohistochemical finding shows positive staining for CD99 (× 100).
C. Fish test of the tumor shows separated signal.

A	B
C	

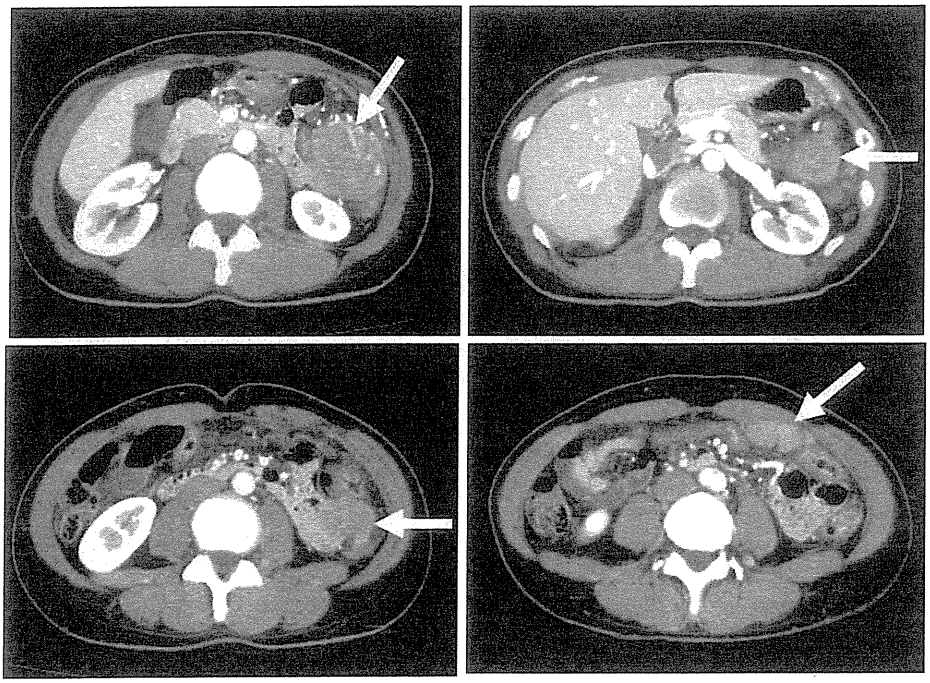

Fig. 3A. Abdominal CT scan shows the main tumor.
B. The disseminated lesion was showed around mesentery.
C. The disseminated lesion was showed on abdominal wall in abdominal CT scan.

A	B
B	C

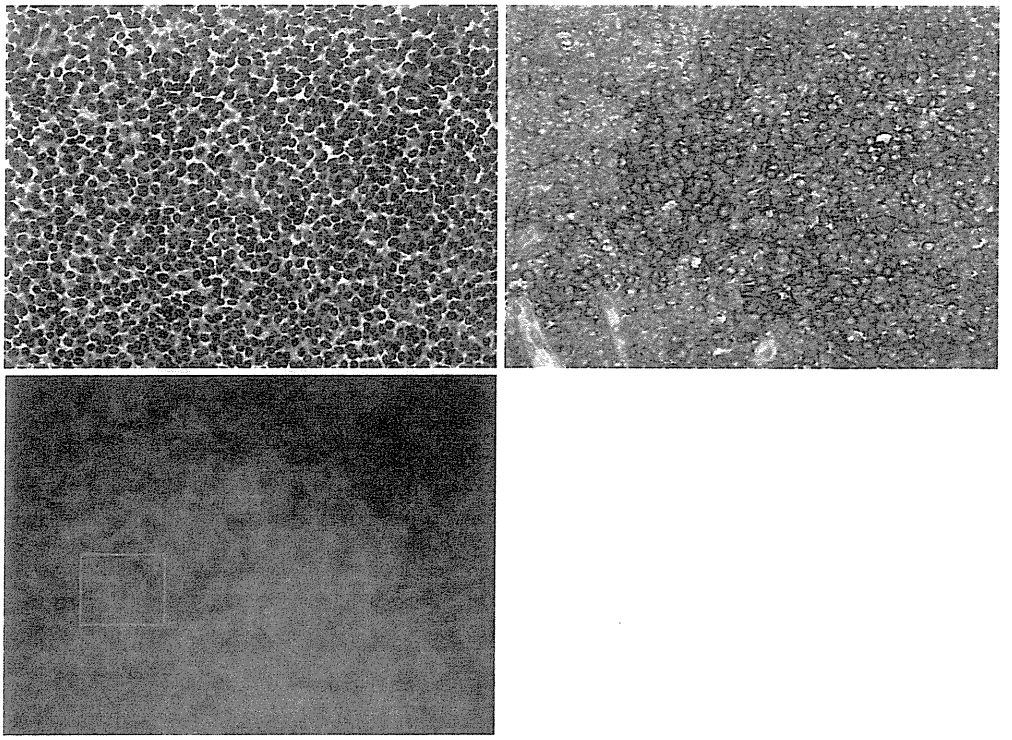

Fig. 4A. The tumor portion was composed of small round cells (H.E. × 400).
B. Immunohistochemical finding shows positive staining for CD99 (× 400).
C. Fish test of the tumor shows separated signal.

A | B
C |

手術所見：腹腔内に少量の血性腹水を認めた．腫瘍は，横行結腸が原発と考えられた皮膜に包まれた多房性腫瘍であり，横行結腸部分切除術を施行し腫瘍を摘出した．

術後病理組織学的検査：腫瘍は一部にmyxomatousな変化や出血を認める，多孔状の腫瘍であった．H.E.染色で特有な構築は認めず均一な小円形細胞が密集していた（**Fig. 2A**）．免疫染色はCD99陽性（**Fig. 2B**），Vimentin陽性で，c-kitは比較的多くの細胞に陽性であった．その他，サイトケラチンAE1/3，Calretinin，S100，CD34，CD10，CD56，Inhibinαはいずれも陰性であった．また，EWSR1（22q 12）Break probe（POSEIDON）を用いてFISH検査を行ったところ，分離シグナルが検出され(**Fig. 2C**)，ES/pPNETと診断した．

術後経過：高齢であるため術後補助化学療法は行わなかった．術後約1年後の平成23年4月に腹腔内再発に対して再手術を施行した．

症例2：38歳，女性．

主訴：左胸部痛．

現病歴：2010年9月，左胸部痛を主訴に受診．PET検査で左腎腹側にFDGの集積を認める不整な腫瘍を多数認め精査加療目的に当科入院となった．

腹部造影CT検査：左腎臓の腹側に径10cm大の境界明瞭な不整形腫瘍(**Fig. 3A**)と，周囲の腸間膜(**Fig. 3B**)，腹壁にも多数の腫瘍を認めた（**Fig. 3C**)．

以上より腹膜播種を伴うGISTが強く疑われた．主腫瘍が10cmと大きく，確定診断を行う意味も含め手術を施行した．

手術所見：腹腔内に少量の血性腹水を認めた．腫瘍は横行結腸脾彎曲部から発生した径10cmの柔らかい腫瘍であり，腸間膜，大網，腹壁に播種病変を認めた．横行結腸部分切除術にて腫瘍を摘出し，播種病変は可及的に切除した．

術後病理組織学的検査：H.E.染色でNC比の大きい比較的小型で均一な細胞が瀰漫性に増生した（**Fig. 4A**)．免疫染色はCD56，CD99（**Fig. 4B**)，synaptophysin，CD57，NSE陽性で，CD3，CD20，AE1/AE3，EMA，Desmin陰性であった．S-100 protein，LCA，CK7陰性であった．症例1と同様にEWSR1（22q 12）Break probe（POSEIDON）を用いてFISH検査を行ったところ，分離シグナルが検出され(**Fig. 4C**)，ES/

Table 1. Cases of Japanese ES/pPNET arising from the abdominal cavity

Age/Sex	Symptom	Origin	Size (cm)	Therapy	Prognosis	Recurrence
41/M	Hypogastralgia	Omentum	7.0×5.0	Partial resection Chemotherapy	4M/Death	Local recurrence Dissemination
40/M	Hypogastralgia	Small intestinal mesentery	11×8.0	Partial resection Chemotherapy	7M/Death	Local recurrence Dissemination
24/F	Hypogastralgia	Small intestinal mesentery /Peritoneum	6.0	Surgery Chemoradiation	10M/Death	Dissemination
52/M	Abdominal distention	Mesentery	13×12	Resection	5M/Death	Dissemination
37/M	Abdominal distention	Pelvis/Omentum	Unknown	Partial resection	Unknown	Dissemination
24/F	Abdominal distention	T-colon	12×10	Resection	20M/Survival	None
49/M	Hypogastralgia	Small intestinal mesentery	3.5×2.0	Partial resection	1M/Death	Dissemination
41/M	Hypogastralgia	Small intestinal mesentery	9.0×8.0	Probe laparotomy	1M/Death	S-colon/Sacrum Invasion
59/M	Abdominal mass	D-colon	11	Resection	7M/Death	Local recurrence Dissemination
20/F	Epigastralgia	Small intestinal mesentery	15×13	Bypass surgery Radiation	2M/Death	Dissemination
78/F	Chest pain	T-colon mesentery	13×8.0	Total resection	12M/Survival	Local recurrence Dissemination
38/F	Chest pain	T-colon mesentery	9.4×7.5	Total resection Chemotherapy	12M/Survival	None

pPNET と診断した.

術後補助化学療法：VDC-IE (Vincristine+Cyclophosphamide+Doxorubicin+Ifosfamide+Etoposide) による術後補助化学療法を 8 コース施行した. 術後 1 年の現在, 再発を認めず経過良好である.

考　察

ES は, 1921年に小児や若年者の骨を原発とした未分化な小円形細胞からなる悪性腫瘍として Ewing により最初に報告された[1]. その後, 骨原発性の ES の病理組織によく似た組織像を示す軟部腫瘍を骨外 ES として1975年 Angervall&Enzinger らが報告した[2]. 一方, 1918年に Stout によって花冠状構造を伴った尺骨原発の小円形細胞腫瘍が報告された後[3], 軟部組織の神経外胚葉への分化を特徴とする腫瘍として末梢性未分化神経外胚葉性腫瘍 Peripheral primitive neuroectodermal tumor (pPNET) の存在が報告されるようになった[4]. しかし, これらの腫瘍は, 近年の染色体分析や分子生物学の進歩によって骨原発性 ES, 骨外原発性 ES, pPNET, また Askin 腫瘍でも t(11；22)(q24；q12) などの共通の染色体転座を有することが明らかになり[5], これらは一連の疾患として, 新 WHO 分類 (2002年) において ES と PNET は種々程度に神経外胚葉への分化を示す円形細胞からなる同一の腫瘍と定義され ES/pPNET として 1 項目に認識されるようになった[6]. また, 発生部位も骨や軟部組織だけでなく全身のあらゆる臓器から生じることが明らかになってきている.

軟部組織腫瘍の中で ES/pPNET の発生は 4～7％とまれであり[7][8], 腹腔内原発の ES/pPNET は本邦報告が10例と極めてまれな疾患である[9]. 自験例を含めた12例の検討では, 男女比は 7：5, 平均年齢は41.9歳(20～78歳)であり, 従来の ES/pPNET が小児から若年者に多く発生するのに比べて高齢で発生している. ES/pPNET の主な症状は腹痛, 腹部膨満感などの腫瘍の増大に関連した症状であるが, 小腸穿孔や腸重積による症状も認められている. 発生部位, 腫瘍最大径, 腹膜播種に関しては現在までに報告されているものと同様であった. 治療に関しては, 外科的切除術が全例に施行されているが, 多くは部分切除術であった. 術後追加治療としては, 術後補助化学療法や放射線療法が施行されていた. 予後に関しては, 完全切除された 1 例を除いて10カ月以内に死亡しており予後不良であった (**Table 1**). しかし, われわれの症例は 2 例とも術後経過 1 年以内と短いが, 症例 1 では再発を認めているが存命中であり, 症例 2 は再発を認めず経過中である. 最近国内で, 限局性 Ewing Sarcoma Family Tumor (ESFT) に対する VDC-IE 療法の臨床試験や再発, 転移を有した ESFT 症例への Irinotecan+cisplatin 併用療法等の複数の臨床試験が進行中であり, エビデンスとして確立されたものではないが, ES/pPNET に対する治療は, 初回手術での完全切除は勿論重要であり, 術後補助化学療法や放射線治療などの

集学的治療が必要であると考える．また，完全切除が可能な状態での早期発見が望まれるため腹腔内原発のES/pPNETという疾患はまれではあるが腹腔内腫瘍の鑑別に挙げることも必要であると思われる．

結　語

腹腔内原発の極めてまれなES/pPNETを2例経験したので文献的考察を加え報告した．

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TWO CASE REPORTS OF EWING SARCOMA WITH PERIPHERAL PRIMITIVE NEUROECTODERMAL TUMOR (ES/pPNET) ARISING FROM ABDOMINAL CAVITY

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We report two rare cases of Ewing sarcoma with peripheral primitive neuroectodermal tumor (ES/pPNET) arising from the abdominal cavity in a 78-year-old female patient and a 38-year-old female patient. In Japan, ES/pPNET arising from the abdominal cavity is a very rare disease. We could only find 10 reports in Japan. We experienced two such cases, and put these dates in order and suggest that perfect surgical resection is very important together with postoperative chemotherapy.

Key words : Ewing sarcoma, pPNET, intraabdominal tumor

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ORIGINAL ARTICLE

The Kampo medicine, Goshajinkigan, prevents neuropathy in patients treated by FOLFOX regimen

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Abstract
Background Oxaliplatin is now considered a standard treatment for advanced or unresectable colorectal cancer, but its main dose-limiting toxicity is sensory neuropathy. The OPTIMOX (stop and go) approach offers a reasonable strategy, but the preventive agent is not established. It is reported that the Kampo medicine, Goshajinkigan (GJG), has recently been considered an effective agent for the neuropathy of taxanes and for vibration sensation in patients with diabetic neuropathy. The aim of this study was to clarify the efficacy of GJG for peripheral neuropathy associated with oxaliplatin therapy.
Patients and method From 2007, 45 patients treated with modified FOLFOX6 for non-resectable or recurrent colorectal cancer participated in the study. Twenty-two patients (GJG group) received oral administration of 7.5 g/day of GJG every day during mFOLFOX6 therapy and 23 patients (control group) did not receive GJG. Neuropathy was evaluated during every course according to DEB-NTC (Neurotoxicity Criteria of Debiopharm).
Results The median number of cycles per patient in the GJG group was 13 (range 4–32), and in the control group was 12 (range 4–28). The cumulative dose of oxaliplatin was 1105 mg/m^2 (GJG group) and 1120 mg/m^2 (control group). The incidence of grade 3 peripheral neuropathy in the GJG group was significantly lower than in the control group ($p < 0.01$, log-rank test). The incidence of grade 3 peripheral neuropathy after 10 courses was 0% in the GJG group and 12% in the control group, and after 20 courses was 33% in the GJG group and 75% in the control group. The percentage of grade 2 and 3 peripheral neuropathy in the GJG group was lower than that in the control group. There were no differences in adverse effects between the two groups except for peripheral neuropathy and influence on tumor response.
Conclusion The Kampo medicine, Goshajinkigan, is useful in preventing neuropathy in non-resectable or recurrent colorectal cancer patients treated with a FOLFOX regimen.

Keywords Neuropathy · Kampo medicine · Goshajinkigan · Oxaliplatin · Colorectal cancer

Introduction

Oxaliplatin, a third-generation platinum analog, has demonstrated efficacy as first-line chemotherapy in metastatic colorectal cancer [1] and as adjuvant therapy [2]. Although all platinum analogs are potentially neurotoxic, oxaliplatin is associated with a unique spectrum of neurologic symptoms. Acute neuropathy develops immediately after infusion, characterized by cold-exacerbated paresthesia, muscle spasms, and fasciculations [1, 3]. Although acute symptoms typically resolve within a week, at higher cumulative doses oxaliplatin induces dose-limiting sensory neuropathy leading to sensory ataxia and functional impairment [1, 3]. Severe oxaliplatin-induced neuropathy occurs in 10–20% of

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patients receiving over 750–850 mg/m^2 [1, 2]. Neuropathy limits treatment tolerability, often necessitating treatment delay or cessation, and neuropathic symptoms may persist for a long time [4, 5].

The OPTIMOX (stop and go) approach [6] offers a reasonably good strategy, but attempts to prevent oxaliplatin-induced neuropathy have not been successful. Gamelin et al. [7, 8] reported that administration of calcium gluconate and magnesium sulfate (Ca/Mg) before and after oxaliplatin therapy could alleviate peripheral neurotoxicity. Other similar treatments have been described, including glutathione [9], *N*-acetylcysteine [10], xaliproden [11], carbamazepine [12], or glutamine [13], but a preventive agent for oxaliplatin-induced neuropathy has not yet been established. The Kampo medicine, Goshajinkigan (GJG), is composed of 10 natural ingredients and is classified as a drug that affects sensory nerves [14, 15]. Some studies suggested that GJG improved taxanes-induced neuropathy [16] and vibration sensation in patients with diabetic neuropathy [17]. Recently, Kono et al. [18] reported in a retrospective study that GJG was effective for peripheral neurotoxicity of oxaliplatin in patients with advanced or recurrent colorectal cancer.

We conducted the present prospective randomized study to confirm the efficacy of GJG for preventing oxaliplatin-induced peripheral neuropathy in patients with non-resectable or recurrent colorectal cancer who received modified FOLFOX6 (mFOLFOX6) therapy. The aim of this study was to clarify the efficacy of GJG for peripheral neuropathy associated with oxaliplatin therapy.

Materials and methods

Patients

In a study that investigated the neuropathy of various agents, including oxaliplatin, the incidence of more than grade 2 (National Cancer Institute's Common Toxicity Criteria; NCI-CTC) neuropathy was 5% in the Ca/Mg group and 54% in the control group when the mean total dose of oxaliplatin was 500–550 mg/m^2 (equivalent to six cycles at an oxaliplatin dose of 85 mg/m^2) [7]. The number of patients required to reproduce these results was calculated using a type I error (a) of 0.05, a type II error (b) of 0.2, and a control-to-treated data number ratio of 1:1. Therefore, the number of subjects for this study was set at 45 to allow for a 10% dropout rate. From January 2007 to December 2009, a total of 45 advanced or recurrent colorectal cancer patients who received mFOLFOX6 therapy at Tokushima University Hospital were eligible for this study. Patients signed the consent form and fulfilled the following criteria before treatment: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, normal bone marrow function (white blood count $\geq$4000/mm^3, platelet count $\geq$100000/mm^3), liver function (serum total bilirubin <1.5 mg/dl), renal function (creatinine <1.5 mg/dl), and heart function (stable cardiac rhythm, no active angina, no clinical evidence of congestive heart failure). Patients were excluded from the study if they had clinical neuropathy, diabetes mellitus, alcoholic disease, or brain involvement, or if they were on vitamin B, magnesium or calcium therapy. Clinical data was collected as follows; age, gender, performance status, primary tumor site, metastatic tumor site, and details of mFOLFOX6 therapy (previous chemotherapy, use of bevacizumab, number of courses, cumulative oxaliplatin dose). Informed consent was obtained from all patients included in the study, which was approved by local ethics committees. This study was registered in UMIN (000002494).

Treatment plan

Therapy was administered on an outpatient basis and patients were premedicated with appropriate antiemetics. Patients were randomly assigned to receive mFOLFOX6 therapy with GJG (GJG group) or without (control group). Random allocation of participants to GJG group or control group was performed by a person not involved in the care or evaluation of the patients. GJG (7.5 g/day divided into 2–3 doses) (Tsumura and Co., Japan), was administered during mFOLFOX6 therapy, given orally before meals or between meals on a daily basis. Other sensory neuromodulatory agents such as calcium–magnesium infusions or antiepileptic-like agents were forbidden. The mFOLFOX6 chemotherapeutic regimen consisted of a 2-h intravenous infusion of oxaliplatin (85 mg/m^2) combined with l-LV (100 mg/m^2), followed by a rapid intravenous infusion of 5-FU (400 mg/m^2), and then a 46-h continuous infusion of 5-FU (2400 mg/m^2). This regimen comprised one course of therapy and was repeated once every 2 weeks.

Patient evaluation

Patients enrolled in this study were evaluated at baseline (prior to chemotherapy) and before each course of treatment. The differences between the two groups, GJG group and control group, were evaluated as follows: the incidence of grade 3 peripheral neuropathy, the number of patients in each course, the percentage of grade 2 and 3 peripheral neuropathy in each course, adverse effects (grade 3) except for neuropathy, and influence of tumor response to mFOLFOX6. Peripheral neuropathy evaluations were based on the Neurotoxicity Criteria of Debiopharm (DEB-NTC) [19]. If patients had grade 3 neuropathy, the oxaliplatin dose was reduced to 75% of the previous dose. Adverse effects of

grade 3 except for neuropathy were assessed using the NCI-CTC. Chemotherapy was delayed until recovery if the neutrophil count decreased to less than 1500/L or the platelet count decreased to less than 100000/L. 5FU and oxaliplatin doses were reduced when NCI-CTC grade 3 or 4 non-neurological toxicity occurred. The anti-tumor effect of chemotherapy was assessed by the Guidelines for Evaluation of the Response to Treatment in Solid Tumors (RECIST) [20].

Data analysis

The primary end point of this study was the incidence of grade 3 peripheral neuropathy. The secondary end points were the percentage of grade 2 and 3 peripheral neuropathy in each course, adverse effects except for neuropathy, and tumor response to mFOLFOX6. The assessment of the occurrence of peripheral neuropathy was based on Kaplan–Meier analyses. The two groups were compared with the log-rank test to identify differences in the incidence of peripheral neuropathy. The chi-squared test was used to assess differences in incidence of grade 3 peripheral neuropathy at each course between the two groups. Quantitative data were given as median (range). Comparisons of other clinical data were performed using a chi-squared test, Fisher's exact probability test or Mann–Whitney U test, as appropriate. All statistical tests performed were two-sided and declared at the 5% significance level. All statistical analysis was performed using StatMate version 3 software (Japan).

Results

Patient characteristics

All patients were randomly allocated to the GJG group ($n = 22$) or the control group ($n = 23$). The population in the GJG group consisted of 14 men and 8 women with a median age of 67. The population in the control group consisted of 8 men and 15 women with a median age of 65. The majority of patients in the two groups were PS 0 and 1. The primary tumor sites in the GJG group were 15 colon and 7 rectum, and those in the control group were 16 colon and 7 rectum. The metastatic site was similar in the two groups. There was no statistically significant difference between the two groups based on any of these parameters. The patients' characteristics are listed in Table 1.

Details of mFOLFOX6 therapy

The details of mFOLFOX6 therapy are listed in Table 2. The presence of previous chemotherapy treatment and the use of bevacizumab were similar in the two groups. The median number of chemotherapy courses was 13 (range 4–32) in the GJG group and 12 (range 4–28) in the control group. The median cumulative oxaliplatin (L-OHP) dose was 1105 mg/m^2 (range 340–2720) in the GJG group and 1120 mg/m^2 (range 340–2380) in the control group. There was no statistically significant difference between the two groups based on any of these parameters. In the GJG group, 13 patients discontinued chemotherapy; nine showed progressive disease and four patients experienced an allergic reaction to oxaliplatin. In the control group, 11 patients discontinued chemotherapy; nine showed progressive disease, one had an allergy to oxaliplatin and one patient complained of persistent grade 3 oxaliplatin-induced neuropathy.

Table 1 Patient characteristics

	GJG	Control	p value
n	22	23	
Age	67 (48–77)	65 (52–80)	0.21
Sex			
Male	14 (64%)	8 (35%)	0.1
Female	8 (36%)	15 (65%)	
Performance status			
0	9 (41%)	10 (43%)	0.87
1	10 (45%)	11 (48%)	
2	3 (14%)	2 (9%)	
Primary tumor			
Colon	15 (68%)	16 (70%)	0.82
Rectum	7 (32%)	7 (30%)	
Metastatic site			
Liver	12 (54%)	12 (53%)	0.84
Lung	3 (14%)	4 (17%)	
Local	3 (14%)	1 (4%)	
Lymph node	2 (9%)	3 (13%)	
Other	2 (9%)	3 (13%)	

Table 2 Details of FOLFOX therapy

	GJG ($n = 22$)	Control ($n = 23$)	p value
Previous treatment			
Yes	4 (18%)	4 (17%)	0.75
No	18 (82%)	19 (83%)	
Use of bevacizumab			
Yes	18 (82%)	18 (78%)	0.94
No	4 (18%)	5 (22%)	
No. of courses	13 (4–32)	12 (4–28)	0.87
Cumulative L-OHP dose (mg/m^2)	1105 (340–2720)	1120 (340–2380)	0.87

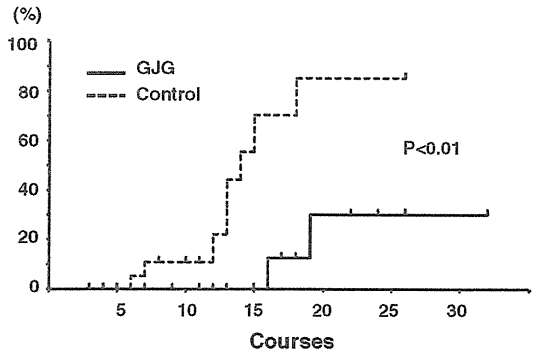

Fig. 1 Kaplan–Meier analyses showed that the incidence of grade 3 peripheral neuropathy occurred significantly less frequently in the GJG group than the control group ($p < 0.01$, log-rank test)

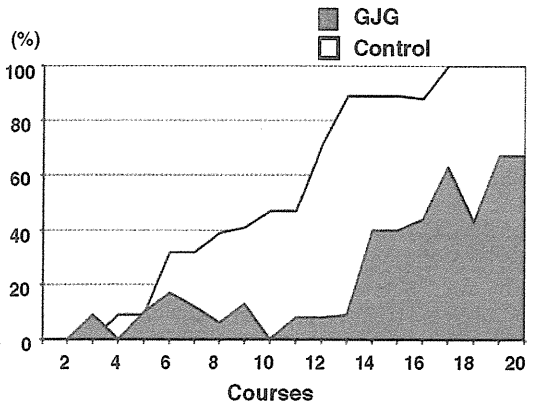

Fig. 2 The percentage of grade 2 and 3 peripheral neuropathy in each cycle was lower in the GJG group than the control group

Effect of GJG on neuropathy

The compliance in the GJG group was 100%. Compliance was checked on the starting day of each course. The number of patients in each course was similar in the two groups. Kaplan–Meier analyses showed that the incidence of grade 3 peripheral neuropathy occurred significantly less frequently in the GJG group than the control group ($p < 0.01$, log-rank test). The incidence of grade 3 peripheral neuropathy after 10 courses was 0% in the GJG group and 12% in the control group, and after 20 courses was 33% in the GJG group and 75% in the control group (Fig. 1). There was no statistically significant difference between the two groups in regard to the incidence of grade 1 or worse and grade 2 or worse peripheral neuropathy (data not shown). The percentage of grade 2 and 3 peripheral neuropathy in each course was lower in the GJG group than the control group (Fig. 2).

Adverse effects and influence on tumor response

Table 3 summarizes adverse effects (grade 3) except for neuropathy. There were no chemotherapy-related deaths during the study. The main toxicities were neutropenia, nausea and diarrhea. In regard to tumor response to mFOLFOX6, no complete response was observed in either group. A partial response was observed in 15 patients (68%) in the GJG group and in 13 patients (57%) in the control group. Stable disease was observed in 5 patients (23%) in the GJG group and in 8 patients (35%) in the control group. The response rate (complete response and partial response) and the disease control rate (complete response, partial response and stable disease) were 68 and 91% in the GJG group and 57 and 92% in the control group, respectively. There were no statistically significant differences in incidence and severity of adverse effects except for peripheral neuropathy and influence on tumor response to mFOLFOX6 between the two groups. The tumor response to mFOLFOX6 is shown in Table 4.

Table 3 Adverse effects (grade 3) except for neuropathy

	GJG ($n = 22$)	Control ($n = 23$)	p value
Neutropenia	3 (14%)	1 (4%)	0.27
Anorexia	0 (0%)	1 (4%)	0.32
Nausea	4 (18%)	2 (9%)	0.34
Vomiting	1 (5%)	1 (4%)	0.97
Diarrhea	2 (9%)	4 (17%)	0.41
Mucositis	2 (9%)	2 (9%)	0.96
All grade 3 toxicity	8 (36%)	8 (35%)	0.84

Table 4 Tumor response to FOLFOX

	GJG ($n = 22$)	Control ($n = 23$)	p value
Tumor response			
Complete response	0 (0%)	0 (0%)	0.86
Partial response	15 (68%)	13 (57%)	
Stable disease	5 (23%)	8 (35%)	
Progressive disease	2 (9%)	2 (8%)	
Response rate	15 (68%)	13 (57%)	0.62
Disease control rate	20 (91%)	21 (92%)	0.96

Discussion

Although the OPTIMOX (stop and go) approach [6] offers a reasonably good strategy, there are several problems, such as the period of use of oxaliplatin and the use of bevacizumab, which are yet to be solved. On the other hand, attempts to prevent oxaliplatin-induced neuropathy have not been sufficiently successful. There are previous randomized controlled studies [9–13, 21] regarding prevention of oxaliplatin-induced neuropathy, including this present report. Five of the seven studies showed the efficacy of the

agent in preventing oxaliplatin-induced peripheral neuropathy. The efficacy of glutamine was reported by Wang et al. [13] and glutathione, a byproduct of glutamine metabolism, was reported by Cascinu et al. [9]. Additionally, Lin et al. [10] reported the efficacy of *N*-acetylcysteine which could increase whole blood concentrations of glutathione in patients with *N*-acetylcysteine supplementation. A major role of glutamine in the prevention of platinum-induced neuropathy has been suggested by several experimental findings. Because glutamine is known to upregulate nerve growth factor (NGF) mRNA in an animal model [22], glutamine supplements may prevent chemotherapy-induced neuropathy via upregulating the NGF level. On the other hand, it has also been hypothesized that high systemic levels of glutamine may downregulate the conversion of glutamine to an excitatory neuropeptide, glutamate, which may also account for the reduced symptoms observed in patients receiving glutamine [23]. Next, a large randomized controlled trial [11] tested xaliproden, a neurotrophic and neuroprotective drug, 11and found that it reduced the risk of grade 3–4 peripheral neuropathy by 39% in metastatic colorectal cancer patients receiving oxaliplatin.

In contrast, two studies of calcium gluconate and magnesium sulfate (Ca/Mg) [21] and carbamazepine [12], the sodium channel blocker, could not show the efficacy of the agent in preventing oxaliplatin-induced peripheral neuropathy. The mechanism of platinum drug neurotoxicity may involve drug accumulation within the peripheral nervous system, especially in the dorsal root ganglia [24]. This suggested that sodium channels may only be involved in acute peripheral neuropathy.

This present study is the first report proving the efficacy of the Kampo medicine, Goshajinkigan, against oxaliplatin-induced peripheral neuropathy using a prospective control study. Neuropathy is the major cause of dose reduction and discontinuation of oxaliplatin treatment [2], with severe neuropathy occurring in 15–20% patients with a cumulative dose of 750–850 mg/m^2 [1, 2]. In the present study, the mean cumulative oxaliplatin dose administered was 1105 mg/m^2 in the GJG group and 1120 mg/m^2 in the control group. Recently, Kono et al. [18] reported in a retrospective study that GJG was effective against peripheral neurotoxicity of oxaliplatin. Additionally, a larger placebo-controlled double-blind randomized phase II study [25] to confirm the usefulness of GJG is taking place in Japan.

A major concern is that GJG might protect tumor cells from the cytotoxic effects of chemotherapy. Although Ca/Mg infusion was suggested to decrease antitumor activity [26], in the current study GJG did not have an influence on tumor response to mFOLFOX6 therapy. Kono et al. [18] reported that the tumor response rate was lower in the group that received GJG + Ca/Mg than in the GJG group and suggested that some interaction might have occurred when GJG and Ca/Mg were combined. Additionally, in the current study GJG did not have an influence on adverse effects except for peripheral neuropathy.

Several mechanisms have been suggested by which GJG may alleviate peripheral neuropathy [27–29]. The first is that GJG promotes the release of dynorphin, and thus improves numbness/pallesthesia via the opiate system. The second is that GJG promotes nitric oxide production, and thus improves the circulation and the blood supply to the nerves. Recently, Joseph et al. [30] reported that oxaliplatin acted on IB4-positive C-fiber nociceptors to induce an oxidative stress-dependent acute painful peripheral neuropathy. Imamura et al. [31] reported that GJG reduced transmitter proteins and sensory receptors associated with C-fiber activation. This effect may be one of the mechanisms of GJG which prevents oxaliplatin-induced neuropathy.

In regard to combination treatment, Kono et al. [18] reported that the patients who received GJG + Ca/Mg developed worse neuropathy than those who received GJG alone and suggested that GJG alone (rather than combined with Ca/Mg) may be more effective in suppressing peripheral neurotoxicity. Although it will be necessary to confirm the usefulness of combination treatment by performing larger prospective studies in the future, a candidate may be either GJG + glutamine or GJG + xaliproden.

The key weaknesses of this report are as follows: no placebo control, no double-blinding and a small sample. However, Kampo medicines in Japan are strictly monitored by means of three-dimensional high-performance liquid chromatography (3D-HPLC), and therefore their reliability is of a high level. We firmly believe that the result of a placebo-controlled double-blind randomized phase II study [25] to confirm the usefulness of GJG reinforces our findings.

Conclusions

The Kampo medicine, Goshajinkigan, safely reduced the incidence of severe neuropathy by mFOLFOX6 regimen without any adverse influence on the response rate to mFOLFOX6. Therefore, Goshajinkigan is useful in preventing oxaliplatin-induced neuropathy in patients with non-resectable or recurrent colorectal cancer.

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Conflict of interest No author has any conflict of interest.

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