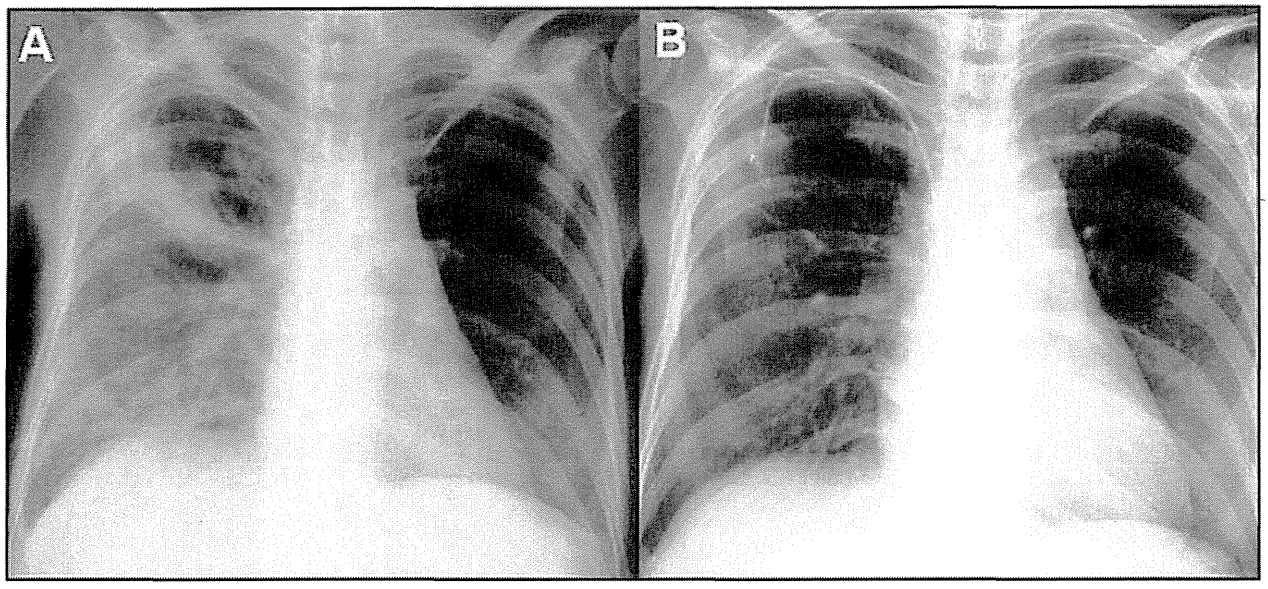

Figure 3. Chest x-ray before and on trastuzumab monotherapy. (A) Lymphangitic pulmonary metastases of right lower lung were suspected. (B) Abnormal finding improved with trastuzumab.

as confirmed by experience with our patient, although patients with diffuse-type gastric cancer are frequently HER2 negative, HER2 status of all gastric cancer types should be evaluated.

Because the ToGA study included chemonaive patients with gastric cancer, the benefit or efficacy of chemotherapy using trastuzumab for patients pretreated with chemotherapy is not currently known. In addition, the antitumor effect of trastuzumab monotherapy is not known. However, trastuzumab monotherapy has been shown to be active with a response rate of 15% in pretreated breast cancer (18% for 3+ IHC),[5] although this is a slightly lower response rate than for monotherapy in chemonaive breast cancer (35% in 3+ IHC),[7] and trastuzumab monotherapy has been adopted for patients who are not considered suitable for cytotoxic chemotherapy.[3]

In summary, this case was instructive for the following reasons: (1) trastuzumab monotherapy was feasible in this heavily pretreated patient with gastric cancer plus massive ascites, (2) trastuzumab and sufficient supportive care were effective in improving the cancer-related symptoms in this patient, (3) although chemotherapy using trastuzumab may become standard first-line chemotherapy for patients with HER2-positive gastric cancer, trastuzumab may even be effective in the salvage setting.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Invest New Drugs (2012) 30:1224–1231
DOI 10.1007/s10637-011-9648-y

PHASE III STUDIES

Progression-free survival and time to progression as surrogate markers of overall survival in patients with advanced gastric cancer: analysis of 36 randomized trials

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Received: 5 January 2011 / Accepted: 14 February 2011 / Published online: 25 February 2011

Summary Progression-free survival (PFS) and time to progression (TTP) have been reported to correlate with overall survival (OS) in several types of cancers. To our knowledge, however, their use in the evaluation of new agents for AGC has not been investigated. We evaluated the potential of PFS and TTP to act as surrogates of OS in clinical trial settings. Randomized trials of systemic chemotherapy for advanced gastric cancer were identified by comprehensive electronic and manual search. Correlations between PFS/TTP and OS were evaluated. Thirty-six trials with a total of 83 treatment arms and 10,484 patients were selected for analysis. The nonparametric Spearman rank correlation coefficient (ρ) between median PFS/TTP and OS was 0.70 (95% CI, 0.59 to 0.82) and the correlation coefficient between hazard ratios in PFS/TTP and OS was 0.80 (95% CI, 0.68 to 0.92). Correlation tended to be higher in trials reporting PFS (ρ=0.85; 0.72–0.97) than in those reporting TTP (ρ=0.60; 0.24–0.97), trials in Non-Asian countries (ρ=0.80; 0.61–0.99) than Asia (ρ=0.67; 0.39–0.94), trials in patients with measurable lesions only (ρ=0.91; 0.77–1.00) than in those including non-measurable lesions (ρ=0.71; 0.50–0.93), albeit that none of these differences was significant. Our results indicate that improvements in PFS/TTP in advanced gastric cancer strongly correlate with improvements in OS. Further research is needed to clarify the surrogacy of PFS/TTP for OS or the role of PFS as the true end point in future randomized clinical trials of chemotherapy for AGC.

Keywords Chemotherapy · Gastric cancer · Surrogate endpoint · Progression-free survival · Time to progression

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Introduction

Gastric cancer remains one of the most common malignancies and leading causes of cancer death worldwide [1]. The most effective treatment for localized disease is surgery, but approximately half of all patients with advanced-stage disease develop recurrence after curative resection. The prognosis of patients with advanced or recurrent gastric cancer (AGC) remains poor, with median survival times for commonly used combination chemotherapy regimens, consisting of a fluoropyrimidine plus a platinum agent with or without docetaxel or anthracyclines, of only 1 year [2–7]. Trastuzumab, a humanized monoclonal antibody that targets epidermal growth factor receptor 2 (HER2), has recently been shown to improve the prognosis of HER2-positive AGC[7], but these cases account for fewer than 20% of all AGCs. The development of novel anticancer agents for the treatment for AGC is thus urgently required.

The most important issue in the development of new agents for AGC is their ability to prolong survival with acceptable toxicity. This is conventionally evaluated in phase III trials, in which the primary endpoint is usually overall survival (OS). For practical reasons, however, the

use of OS as a primary endpoint may be problematic. In particular, several recent reports have suggested the efficacy of second-line chemotherapy for AGC [8–10], which would potentially lead to underestimation of the effect of new first-line treatment [11].The potential for other clinical endpoints to replace OS as the primary endpoint in randomized trials is therefore of interest: a validated shorter term surrogate endpoint would likely both reduce drug development costs and facilitate the assessment of efficacy.

Progression-free survival (PFS) and time to progression (TTP) have been evaluated as surrogate endpoint of OS in several types of cancers [12–16], and are considered acceptable surrogate endpoints for colorectal cancer and breast cancer [17]. To our knowledge, however, their use in the evaluation of new agents for AGC has not been investigated.

Here, we conducted a comprehensive analysis to determine whether PFS and TTP are correlated with OS in AGC, and whether improvements in PFS and TTP are associated with improvements in OS.

Materials and methods

Search for studies

We conducted a literature search for trials through computer-based searches of the Medline database (January 1966 and June 2010) and of abstracts from conference proceedings of the American Society of Clinical Oncology (1995–2010) and European Cancer Conference and European Society for Medical Oncology (1995–2009). To avoid publication bias, both published and unpublished trials were identified. Search keywords included: "gastric cancer," "randomized" "advanced or metastatic," and "chemotherapy." The search was also guided by a thorough examination of reference lists of original and review articles. No limitation based on language was defined. We included abstracts or unpublished data if sufficient information on study design, characteristics of participants, interventions and outcomes was available.

Procedures

Two investigators (KS and KM) abstracted the data in accordance with the Quality of Reporting of Meta-analyses (QUORUM) guidelines [18]. Randomized trials of systemic chemotherapy for patients with histologically confirmed advanced or recurrent gastric cancer (metastatic disease or unresectable locally advanced disease) of the stomach or gastroesophageal junction were included in the analysis. Trials which compared chemotherapy with best supportive care were also included, as were those which included patients with adenocarcinoma of the distal esophagus. Eligibility was limited to trials which reported data on OS with either or both PFS and TTP.

Exclusion criteria included trials designed to assess combined modality treatments, including radiotherapy and surgery (neoadjuvant or adjuvant chemotherapy); those in which patients were pretreated with chemotherapy; and, to evaluate the risk reduction with chemotherapy for PFS/TTP or OS, those which did not report either hazard ratios (HRs) or Kaplan-Meier survival curves.

For each trial, the following information was extracted: first author's name; year of publication or report; trial design (randomized phase II or phase III); trial area; number of enrolled patients; and treatment regimens. The following was also extracted if reported: HR and 95% CI for clinical outcome (PFS/TTP and OS); proportion of patients with metastatic disease; proportion of patients with measurable lesions; and proportion of patients who received post-protocol chemotherapy.

All data were checked for internal consistency. Disagreements were resolved by discussions among the investigators. The reference arm in each trial was determined by consensus among three investigators (KS, DT, and TY) if not indicated; all other arms were considered investigational. For trials with more than two treatment arms, we constructed multiple pairs of each investigational arm and the reference arm.

Statistical methods

For each trial, median PFS, TTP, OS, and HR with 95% confidence intervals (CI) were abstracted. If the HR was not provided, we estimated HR and 95% CI as relevant effect measures directly or indirectly from the given data [19]. The nonparametric Spearman rank correlation coefficient (ρ) was used as a measure of correlation between the median PFS/TTP and OS and correlation between HR of PFS/TTP and HR of OS. As the number of subject studies was limited, we applied bootstrap resampling [20] using 10000 bootstrap samples to estimate 95% confidence intervals for correlation coefficients.

To investigate possible reasons for heterogeneity, subgroup analyses were conducted according to test variables (PFS or TTP), trial area (Asian or non-Asian), reported data (before 2006 or after 2006), number of patients (<200 or ≥ 200), registration trial with investigational agents (yes or not), number of chemotherapeutic agents in treatment arm (more agents vs. few agents or same number of agents), or proportion of measurable disease, and proportion of patients who received second-line chemotherapy. In the case of global trials, data were classified as both Asian and non-Asian unless suitable subset analysis results were provided.

Statistical analyses were performed using STATA ver. 10 (Stata Corp LP, College Station, TX, USA). All tests were

two-sided, and *P*-values less than .05 were considered statistically significant.

Results

Selection of studies

A total of 826 potentially relevant reports were identified, of which 717 were initially excluded (Fig. 1). After review of the remaining studies, 36 trials with sufficient data were identified as eligible for this meta-analysis, with a total of 83 treatment arms and 10,484 patients [2–7, 21–50].

Table 1 shows the characteristics of each trial. Eleven were randomized phase II trials and 25 were phase III. By region, 4 were conducted in North or South America, 13 in Europe, 2 in America and Europe, 13 in Asia, and 1 in Australia, while 3 were global. Six trials were registration trial [2, 5–7, 38, 46]. Seventeen trials compared combination chemotherapy with different number of agents (2 or more) and few agents (1 or 2).

Most trials were for metastatic disease, and the median proportion of patients with measurable lesions was 95% (47–100%). More studies reported PFS than TTP, while no trial reported both PFS and TTP. Information on second-line chemotherapy was available in 18 trials [2–7, 28, 30–33, 36, 37, 39, 42, 44, 46, 49]. Subset analysis according to area was reported in one global trial (AVAGAST) [46], and these subset data were accordingly included in analyses which focused on comparing Asian and non-Asian trials.

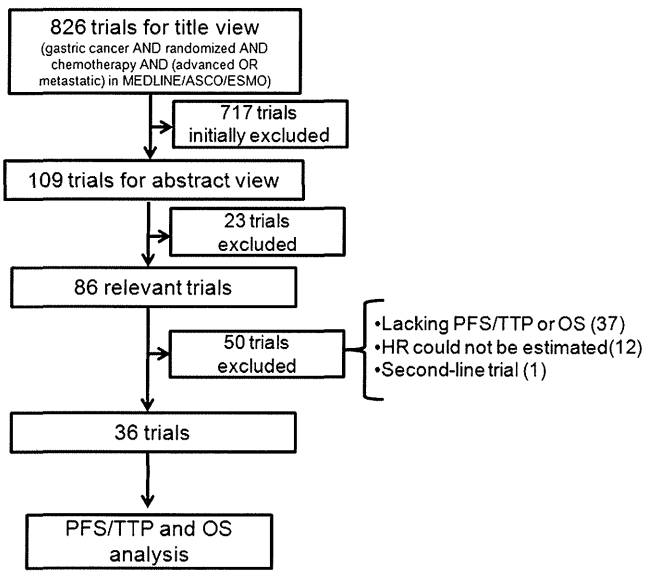

Fig. 1 Selection process for trials

Correlation between PFS/TTP and OS

A moderate correlation was seen between median PFS/TTP and OS, with a ρ value of 0.70 (95% CI, 0.59 to 0.82; $P<0.001$; Fig. 2). Correlations in non-Asian ($\rho=0.79$; 0.69–0.89) and Asian trials ($\rho=0.75$; 0.54–0.95; Fig. 3) were similar.

Correlation between HR for PFS/TTP and OS

A total of 50 pairs of HRs for PFS/TTP and OS between treatment arms were available from the 36 trials, being reported in 19 trials and estimated in 17. A close correlation between HRs for PFS/TTF and OS was seen, with a ρ value of 0.80 (95% CI, 0.68 to 0.92; $P<0.0001$; Fig. 4). No difference in correlation was observed between reported ($\rho=0.80$; 0.60–1.00) and estimated HRs ($\rho=0.82$; 0.67–0.99). Correlation tended to be higher in Non Asian ($\rho=0.80$; 0.61–0.98) than Asian trials ($\rho=0.67$; 0.39–0.94; Fig. 5), higher with registration trials ($\rho=0.94$; 0.60–1.00) and no-registration trial ($\rho=0.79$; 0.64–0.93), higher with comparison of treatment with same number of agents ($\rho=0.89$; 0.76–1.00) than comparison of different number of agents ($\rho=0.75$; 0.54–0.95), higher in trials reporting PFS ($\rho=0.85$; 0.72–0.97) than in those reporting TTP ($\rho=0.60$; 0.24–0.97), and higher in trials in patients with measurable lesions only ($\rho=0.91$; 0.77–1.00) than in those including non-measurable lesions ($\rho=0.71$; 0.50–0.93), albeit that none of these differences was significant. In also, no differences were observed between trials before 2006 ($\rho=0.73$; 0.45–1.00) and after 2006 ($\rho=0.83$; 0.68–0.98), or trials with less than 200 patients ($\rho=0.85$; 0.67–1.00) and with more than 200 patients ($\rho=0.70$; 0.50–0.90).

Discrepancy in HRs for PFS/TTP and second-line chemotherapy

Among the 18 studies with information on second-line chemotherapy, the ratio of the HR of PFS/TTP to that of OS deviated from 1 as the proportion of patients who received second-line chemotherapy increased ($\rho=-0.40$; $P=0.04$; Fig. 6).

Discussion

To our knowledge, this is the first study to evaluate whether PFS and TTP can be used as surrogate endpoints for randomized studies of first-line chemotherapy for AGC. Our results showed that an improvement in PFS/TTP was closely associated with an improvement in OS. Although no consensus on what defines a valid surrogate endpoint has yet been reached, any candidate must correlate to the

Table 1 Baseline characteristics of patients in the 36 included trials

Author	Year	Phase	Region	Treatment arms	No. of patients	Origin	Metastatic disease (%)	Measurable disease (%)	Endpoint (TTP/PFS)	Information on second-line treatment
Cullinan [21]	1985	III	Am	FU vs FU+ADM vs FU+ADM+MMC	151	G	NR	47	TTP	NR
Kim [22]	1993	III	A	FU vs FAM vs FU	324	G	NR	56	TTP	NR
Cullinan [23]	1994	III	Am	FU vs FAP vs FAMe vs FEMe+TZT	252	G	NR	84	TTP	NR
Loehrer [24]	1994	III	Am	FU vs epirubicin vs FU+epirubicin	165	G	63	69	TTP	NR
Pyrhonen [25]	1995	III	E	BSC vs FAMTX	41	G	71	NR	TTP	NR
Kondo [26]	2000	III	A	FU vs Doxifluridine	86	G	NR	NR	TTP	NR
Vanhoefe [27]	2000	III	E	ELF vs CF vs FAMTX	399	G	84	63	PFS	NR
Ohtsu [28]	2002	III	A	FU vs CF vs UFTM	280	G	86	96	PFS	Yes
Ross [29]	2002	III	E	ECF vs MCF	574	E,GEJ,G	57	95	PFS	NR
Tebbutt [30]	2002	III	E	FU vs FU+MMC	254	E,GEJ,G	57	94	PFS	Yes
Bouché [31]	2004	II	E	FU+FA vs CF+FA vs FU+FA+irinotecan	134	G	100	100	PFS	Yes
Pozzo [32]	2004	II	E	FU+FA+irinotecan vs irinotecan+CDDP	146	GEJ, G	94	90	TTP	Yes
Ajani [33]	2005	II	Am	DC vs DCF	155	GEJ, G	95	79	PFS	Yes
Moehler [34]	2005	II	E	ILF vs ELF	114	GEJ,G	100	100	PFS	NR
Thuss-Patience [35]	2005	II	E	DF vs ECF	90	G	98	96	TTP	NR
Van custem [2]	2006	III	E, Am	CF vs DCF	445	GEJ, G	97	100	TTP	Yes
Chin [36]	2007	III	A	S1 vs S1+irinotecan	315	G	NR	57	PFS	Yes
Cunnningham [3]	2008	III	E	ECF vs ECX vs EOF vs EOX	1002	E,GEJ,G	74	100	PFS	Yes
Al-Batra [37]	2008	III	E	FLP vs FLO	220	GEJ,G	94	89	PFS	Yes
Dank [38]	2008	III	E	CF+FA vs ILF	333	GEJ,G	96	NR	TTP	NR
Ikeda [39]	2008	II	A	CF vs S1+DOC	49	G	100	100	PFS	Yes
Jeung [40]	2008	II	A	DOC+CDDP vs S1+DOC	80	G	79	100	PFS	NR
Koizumi [4]	2008	III	A	S1 vs S1+CDDP	305	G	100	63	PFS	Yes
Lee [41]	2008	II	A	S1 vs Capecitabine	91	G	100	100	TTP	NR
Park [42]	2008	II	A	ILF vs PILF	91	G	100	100	PFS	Yes
Ridwelski [43]	2008	III	E	DOC+CDDP vs FLC	270	G	90	100	TTP	NR
Boku [44]	2009	III	A	FU vs S1 vs irinotecan+CDDP	704	G	NR	75	PFS	Yes
Kang [5]	2009	III	A, E, Am	FP vs XP	316	G	100	100	PFS	Yes
Lee [45]	2009	III	A	FP vs Haptoplatin+FU	174	G	94	90	TTP	NR
Ajani [6]	2010	III	E, Am	FP vs S1+CDDP	1053	GEJ,G	96	96	PFS	Yes
Bang [7]	2010	III	A, E, Am	XP vs XP+trastuzumab	584	GEJ,G	96	90	PFS	Yes
Kang [46]	2010	III	A, E, Am	XP vs XP+bevacizumab	774	GEJ,G	96	79	PFS	Yes
Kishimoto [47]	2010	II	A	S1+paclitaxel vs S1+irinotecan	102	G	100	100	PFS	NR
Sawaki [48]	2010	III	A	S1 vs FU+FA	177	G	100	100	PFS	NR
Moehler [49]	2010	II	E	XP vs XI	118	E,GEJ,G	100	NR	PFS	Yes
Tebbutt [50]	2010	II	Australia	wTCF vs wTX	116	E,GEJ,G	93	98	PFS	NR

Am America; *A* Asia; *E* Europe; *FU* 5-fluorouracil; *ADM* doxorubicin; *MMC* mitomycin C; *CDDP* cisplatin; *FAM* FU+ADM+MMC; *FAP* FU+ADM+CDDP; *FAMe* FU+ADM+methyl lomustine; *TZT* triazinate; *Epi* epirubicin; *BSC* best supportive care; *FAMTX* FU+ADM+methotrexate; *ELF* etoposide+leucovorin+FU; *CF* CDDP+FU; *UFTM* uracil/tegafur+MMC; *ECF* epirubicin+CDDP+FU; *MCF* MMC+CDDP+FU; *FA* folinic acid; *DC* docetaxel+CDDP; *DCF* docetaxel+CDDP+FU; *ILF* irinotecan+leucovorin+FU; *ELF* epirubicin+leucovorin+FU; *DF* docetaxel+FU; *ECX* epirubicin+CDDP+capecitabine; *EOF* epirubicin+oxaliplatin+FU; *EOX* epirubicin+oxaliplatin+capecitabine; *FLP* FU+LV+CDDP; *FLP* FU+LV+oxaliplatin: *DOC* docetaxel; PILF,CDDP+ILF; *FLC* FU+LV+CDDP; *FP* CDDP+FU; *XP* capecitabine+CDDP; *PTX* XI, capecitabine+irinotecan; *wTCF* weekly docetaxel+CDDP+FU; *wTX* weekly docetaxel+capecitabine, *G* gastric; *GEJ* gastroesophageal junction; *E* esophagus; *NR* not reported; *TTP* time to progression; *PFS* progression-free survival

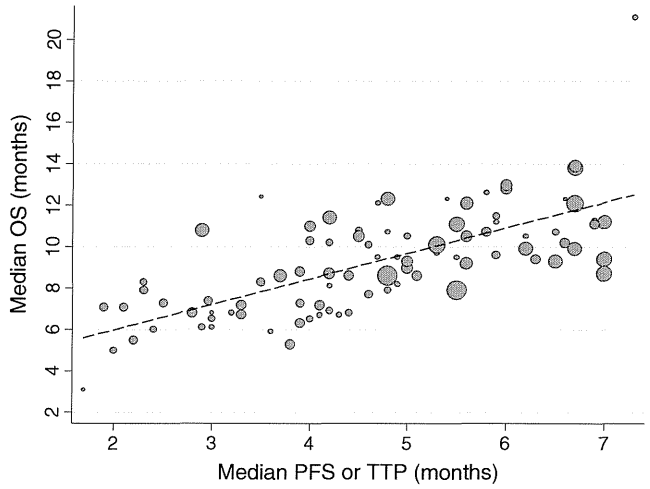

Fig. 2 Median PFS/TTP and OS in 36 trials. The size of the gray markers (*circles*) corresponds to the number of randomized patients in the trial in this analysis. A moderate relationship was seen between median PFS/TTP and OS, with a ρ value of 0.70 (95% CI, 0.59 to 0.82; $P<0.001$)

true endpoint, and effects on the surrogate must correlate to those on the true endpoint [51, 52]. In our analysis, the HR for PFS/TTP showed a significant correlation with that for OS, indicating that the effect of treatment on PFS likely predicts the effect of treatment on OS. In this regard, the coefficient of 0.80 was compatible with that for advanced colorectal cancer, for which PFS is considered an adequate surrogate endpoint in clinical trials [12, 13, 17].

In this analysis we included studies which evaluated either or both PFS or TTP. In their study in patients with advanced colorectal cancer receiving systemic chemotherapy, Tang et al. reported that PFS was more closely correlated with OS than TTP [13]. Although we saw no significant difference between the ρ value of PFS and TTP in our analysis, it nevertheless tended to be higher for PFS, consistent with Tang et al. PFS differs from TTP in that it incorporates death as a result of any cause, in addition to progression. On this basis, PFS might be the better surrogate for OS, as suggested by our results.

Reflecting the relatively high incidence of gastric cancer worldwide, several studies have been performed or are ongoing in various countries or as global studies. A number of differences in AGC between Western and Eastern countries have been identified in tumor characteristics and practice patterns, including surgery or chemotherapy [53]. In Asian trials, the percentage of patients with measurable disease are usually lower than in non-Asian study, which may cause relatively longer survival due to less tumor burden. In also, the proportion of patients who receive second-line chemotherapy is reported to be higher in Asian than western trials. This difference was clearly revealed in the AVAGAST study, where 66% of Asian patients received second-line chemotherapy compared with 31% in Europe and 21% in America [46]. If this difference in second-line chemotherapy contributed to the differences in survival after progression in the various areas, PFS/TTP might be a more sensitive endpoint for future global studies since it might directly reflect the anti-tumor effect of first-line chemotherapy.

In also, our results suggest that the second-line therapy has the potential to underestimate the efficacy of an experimental agent in patients when compared with control patients who receive multiple subsequent therapies. Influence of second-line treatment as crossover might contribute to the non-significant survival differences especially with non-registered trials with approved agents. Additionally, given our finding

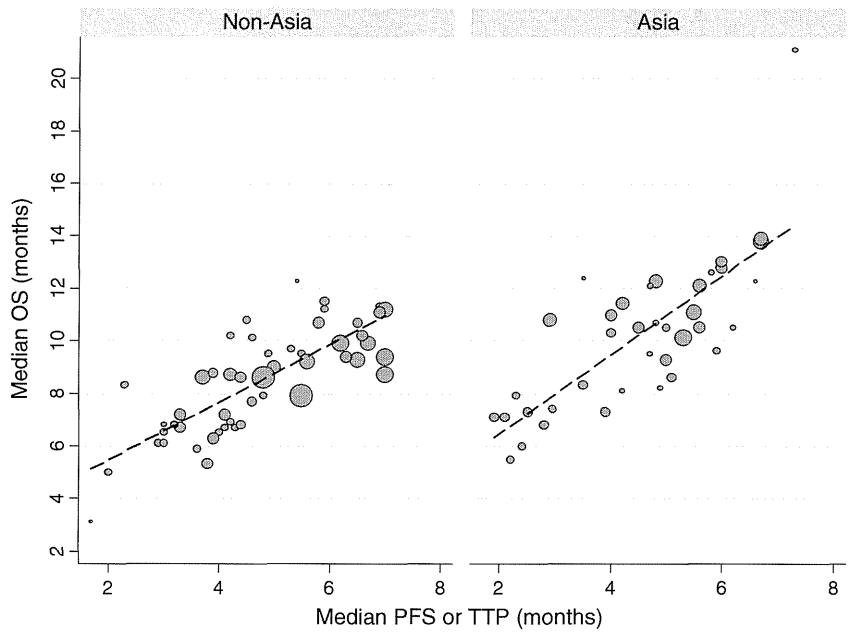

Fig. 3 Median PFS/TTP and OS by trial area. Correlation in non-Asian (ρ=0.79; 0.69–0.89) and Asian studies (ρ=0.75; 0.54–0.95; Fig. 3) was similar

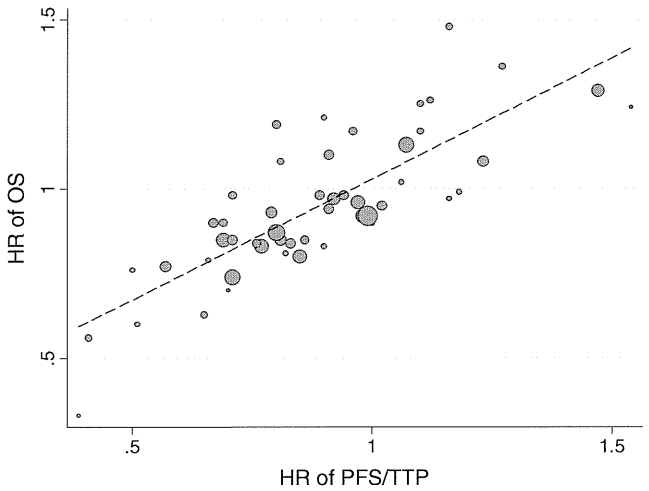

Fig. 4 HR of PFS/TTP and OS in 36 trials. A significant relationship is seen between HRs for PFS/TTF and OS, with the ρ value of 0.80 (95% CI, 0.68 to 0.92; $P<0.0001$)

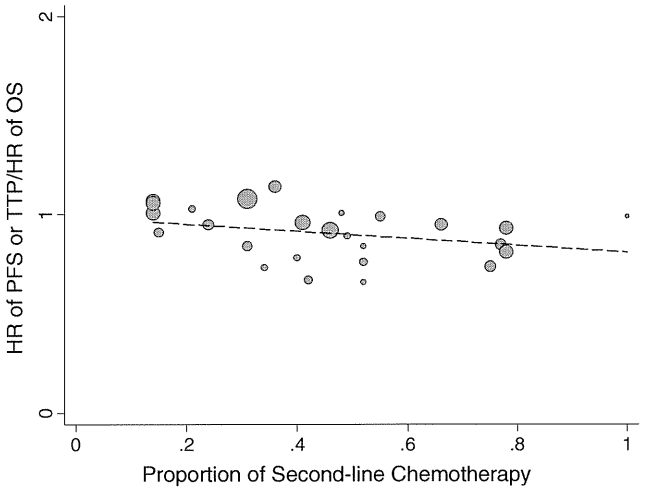

Fig. 6 Discrepancy in HRs for PFS/TTP and second-line chemotherapy. HR of PFS/TTP and HR of OS deviated from 1 in positive proportion to the number of patients who received second-line chemotherapy ($\rho=-0.40$; $P=0.04$)

that studies which included non-measurable lesions tended to have lower ρ values, it might be desirable to restrict entry in studies which use PFS is a primary endpoint to patients with measurable disease, to allow accurate and independent evaluation using standard definitions, such as those by the Response Evaluation Criteria in Solid Tumors Group.

This study has several methodological limitations. First, it was not based on analysis of data from individual patients, which is a better means of evaluating individual-level measures of agreement between the two endpoints (PFS/TTP and OS) [54]. Additional individual data analysis might therefore necessary to confirm the correlation between PFS/TTP and OS. Second, as we did not include trials which did not report HRs or survival curves, a degree of selection bias might be present, albeit that most recent trials did in fact report HR. Third, since not all trials reported information on subset analysis, such as the proportion of measurable lesions or of cases receiving second-line chemotherapy, our results which derive from or refer to these variables were likely insufficient. Accordingly, future trials should ensure that these data are reported. Finally, because most trials provided little information on disease progression, it was impossible to confirm whether the evaluation of this variable had been consistent in each trial arm. Future clinical trials using PFS as a primary endpoint for AGC should ensure that the definition and evaluation of progression be strictly determined.

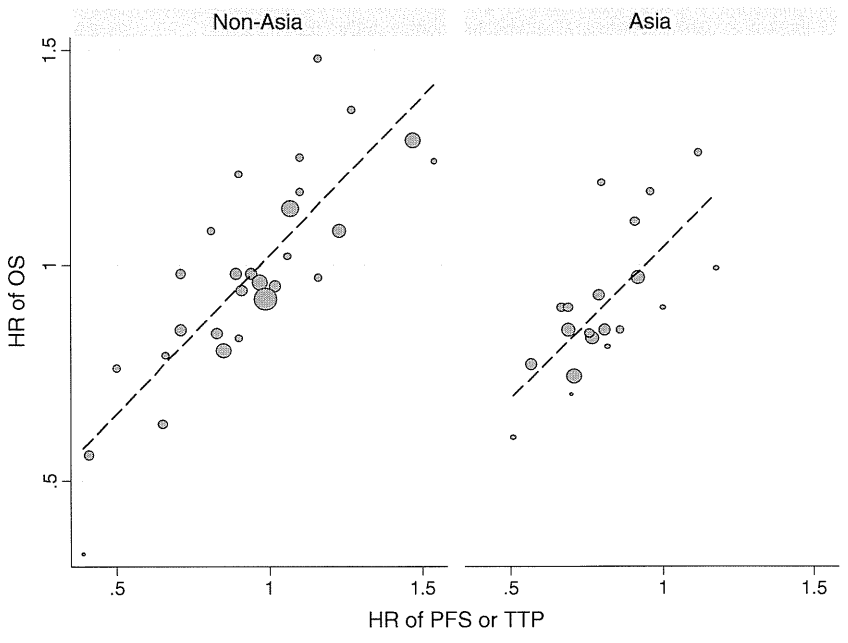

Fig. 5 HR of PFS/TTP and OS by trial area. No significant difference in correlation was observed between Asian ($\rho=0.67$; 0.39–0.94) and non-Asian studies ($\rho=0.80$; 0.61–0.98)

In conclusion, this study shows that improvements in PFS/TTP in AGC are closely associated with improvements in OS. Further research is needed to clarify the surrogacy of PFS/TTP for OS or the role of PFS as the true end point in future randomized clinical trials of chemotherapy for AGC.

Acknowledgements None.

Conflict of interest statement None of the authors have financial or personal conflicts of interest to disclose.

Financial disclosure None.

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発熱性好中球減少症（FN）診療ガイドライン

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編集　日本臨床腫瘍学会

Japanese Society of Medical Oncology
JSMO

Febrile Neutropenia

南江堂

特集　血管新生阻害薬―最新情報のすべて

ベバシズマブ 3)大腸がん治療におけるベバシズマブを含むregimenと期待される血管新生阻害薬*

室　圭**

Key Words：colorectal cancer, angiogenesis, bevacizumab, bevacizumab beyond first progression (BBP), regorafenib

はじめに

大腸がん化学療法において，3種類の抗がん剤，すなわち5-FU系薬剤(5-FU＋LV)，イリノテカン(CPT-11)，オキサリプラチン(L-OHP)がkey drugであり，これら3剤を化学療法の経過中にすべて使い切ることが生存期間延長に最も寄与することが明らかになった[1]．これらに加えて，ここ数年進歩著しい分子標的治療薬が，大腸がん治療にも広く用いられるようになり，標準的治療として組み入れられるようになった．現在，大腸がん領域に臨床導入されている分子標的治療薬は2種類に分けられる．すなわち，angiogenesis系阻害(血管新生阻害)の抗血管内皮細胞増殖因子(vascular endothelial growth factor；VEGF)抗体薬であるベバシズマブと，シグナル伝達阻害の抗上皮成長因子受容体(epidermal growth factor receptor；EGFR)抗体薬であるセツキシマブ/パニツムマブである．大腸がん治療経過中に，これらの薬剤をどのようにしてうまく使い切っていくかがきわめて重要なポイントである．最新のNational Comprehensive Cancer Network (NCCN)のPractice Guideline (Colon Cancer)や，わが国の大腸癌治療ガイドライン[2]では，その治療アルゴリズムの中で，上述の抗がん剤や分子標的治療薬は，いずれも一次治療や二次治療といった順番には関係なく，治療レジメンとして経過中にすべて使い切る形で複数の選択肢が提

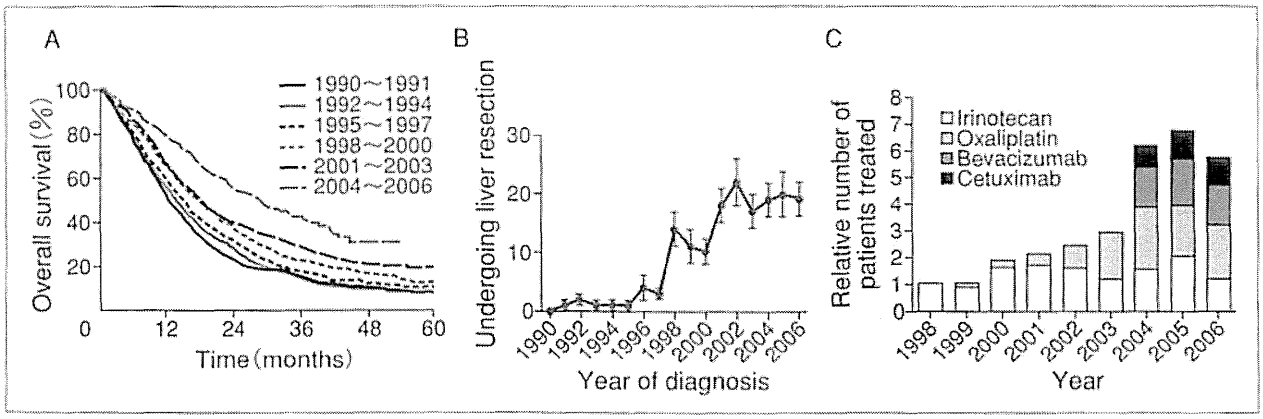

図1　肝切除(conversion)と分子標的薬の導入が進行大腸がんの治療成績向上に大きく寄与(文献[3]より抜粋)

* Bevacizumab and the other angiogenesis inhibitors for metastatic colorectal cancer.

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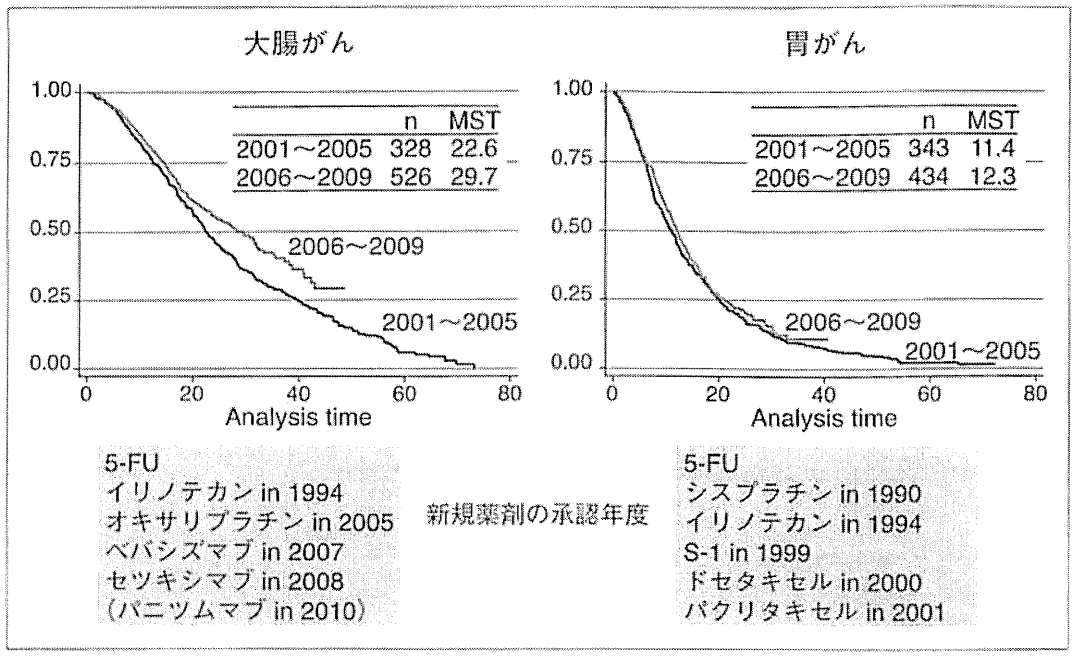

図2　愛知県がんセンター中央病院のデータ（文献[4][5]より抜粋，一部改変）

示されている．

図1-A[3]は，米国の代表的な施設の一つであるMD Anderson Cancer CenterとMayo Clinicにおける大腸がん化学療法症例の治療成績の年次推移を示したものである．1990年以降，年々治療成績の向上が認められおり，特に2004年以降の治療成績が格段によくなっているのがわかる．その理由として，切除不能の状況から切除可能となった，いわゆるconversion（肝切除）例が急速に増加している（図1-B）[3]ことがあげられる．その背景には，近年の化学療法の進歩と切除への意識が高まったことにあると推察される．実際，図1-C[3]に示されているように，2004年以降，従来の抗がん剤に加えて，ベバシズマブを代表とする分子標的治療薬が臨床導入され，化学療法における分子標的薬の役割が増していることが注目すべき点であろう．

以上から，肝切除（conversion）とベバシズマブやセツキシマブの分子標的治療薬の導入が近年の進行大腸がんの治療成績向上に大きく寄与しているものと判断される．

わが国（当院）の実態

前項では，米国のMD Anderson Cancer CenterとMayo Clinicにおける近年の分子標的治療薬導入による大腸がん化学療法の治療成績向上のデータを示した．では，わが国ではどのような状況であろうか．図2は，当院の化学療法例における年代別の大腸がん，胃がんの治療成績を比較したものである．大腸がんに関して，当院の2001～2005年と2006年以降の2つの年代で生存成績を比較したところ，2006年以降の年代での明らかな生存成績向上が確認された[4]．これは，2005年以降にオキサリプラチンや分子標的治療薬であるベバシズマブ，セツキシマブの新規薬剤が臨床導入されたことが大きい．一方，胃がんにおいては，2001～2005年と2006年以降でまったく差を認めず，この10年間で進歩がない現状が浮き彫りになった[5]．これは胃がんで有効な抗がん剤として，5FU系，シスプラチン，イリノテカン，タキサン系とactive drugこそ多く，S-1＋CDDP療法という標準的治療も確立されたものの，2001年パクリタキセル承認以降，新規薬剤の導入が進んでいないことが主要因であると思われる．2011年にHER2陽性胃がんに対するトラスツズマブが承認された．胃がん全体の約15%程度と一部の胃がんではあるが，明らかな生存期間の延長が認められたトラスツズマブの臨床導入により，今後胃がん全体の治療成績向上が図られるかもしれない．

以上から，新規薬剤，特に最近ではベバシズマブを含む分子標的治療薬の臨床導入が，切除

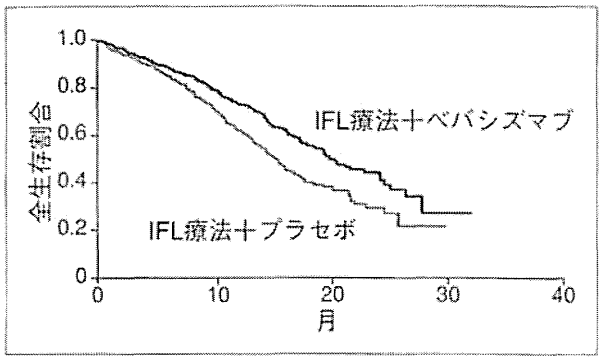

図3　進行・再発大腸がんに対する一次化学療法：AVF 2107g試験　（文献[6]より抜粋，一部改変）

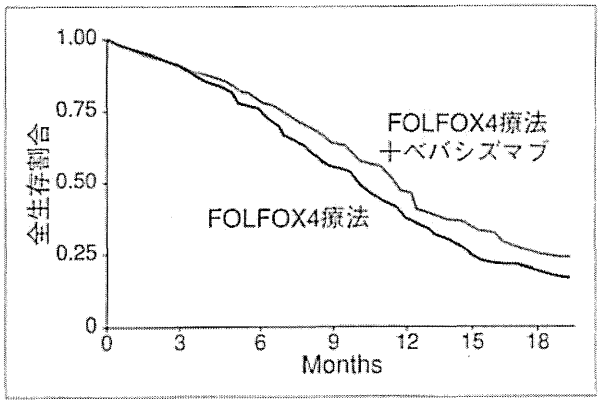

図4　進行・再発大腸がんに対する二次化学療法：ECOG 3200試験　（文献[7]より抜粋，一部改変）

不能進行がんの治療成績向上にとってきわめて重要であるということを強く認識すべきである．

大腸がんにおけるベバシズマブの臨床試験

ベバシズマブの臨床的効果，有用性を示す結果が大腸がんにおいて世界ではじめてHurwitzらによって報告された(AVF2107g試験)[6]．本試験では，進行大腸がんにおける一次治療としてIFL(イリノテカン＋5-FU＋LV)＋ベバシズマブ群(5 mg/kg/2 weeks)とIFL＋プラセボ群の無作為化比較試験(RCT)が，全生存期間(OS)をプライマリーエンドポイントとして行われ，ベバシズマブ群の生存期間中央値(MST)が20.3か月，プラセボ群が15.6か月であり，ベバシズマブによる明らかな生存期間延長が確認された〔hazard ratio(HR)＝0.66, P＝0.00004〕(図3)[6]．その後，5-FU，イリノテカン(IFL)治療後の二次治療として本剤とFOLFOX4(オキサリプラチン＋5-FU＋LV)併用療法のOSにおける有用性も明らかになった(ECOG 3200試験：FOLFOX4＋ベバシズマブ群(10mg/kg/2 weeks)のMST＝12.9か月，FOLFOX4単独群のMST＝10.8か月，死亡に関するHR＝0.75, P＝0.0011)(図4)[7]．さらに，現在一次治療の化学療法として全世界で最も広く行われているFOLFOX(FOLFOX4)療法またはCapeOX〔カペシタビン(capecitabine)＋オキサリプラチン(L-OHP)〕療法にベバシズマブのon/offを比較するRCT(NO16966試験)が行われ，プライマリーエンドポイントの無増悪生存期間(PFS)において，ベバシズマブ併用群がプラセボ群に比較して有意に延長する(9.4か月 vs. 8.0か月，HR＝0.83, P＝0.0023)[8]結果が示された．残念ながらセカンダリーエンドポイントであるOSにおけるベバシズマブ併用群の優越性は検証できなかった．上記試験ではいずれもベバシズマブ群の忍容性は十分良好であったが，本剤に特徴的な毒性である血栓塞栓症・出血・高血圧・蛋白尿・消化管穿孔が認められた．時に致死的となるこれらの毒性には，十分な留意と予測に基づいた臨床的配慮が必要となる．

以上のように，ベバシズマブは化学療法剤との併用により，一次治療と二次治療での有用性が報告され，本剤が大腸がん化学療法のkey drugの一つであるという認識を確固たるものにした．

米国で行われた市販後研究(BRiTE試験)から，ベバシズマブの維持療法の有用性が認められた．すなわち，ベバシズマブを用いた一次治療の増悪(PD)後，二次治療以降にもベバシズマブを継続していく有用性が示唆されたのである(bevacizumab beyond first progression；BBP)[9]．この結果はあくまでもベバシズマブの維持療法のレトロでの市販後研究結果であり，前向き試験ではない．BBPを検証する前向き臨床試験として，ドイツのドイツ癌学会医学腫瘍学協会(AIO)グループがロシュ社のサポートのもと，第III相比較試験(ML18147試験)を行った[10]．図5に本試験の試験デザインを示す．2005年11月からスタートして，最終的に822名が本試験に登録された．これはBBPを検証する二次治療の比較試験であり，二次治療の化学療法レジメンとして，イリノテカンを含むレジメンとしてAIO-IRI, FOLFIRI, CAPIRI or XELIRI, オキサリプラチン併用レジメンとしてFUFOX,

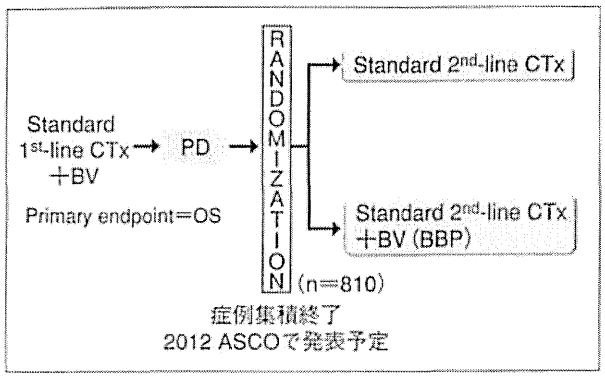

図5　Phase III Trial ML18147(AIO 0504)

FOLFOX, CAPOX or XELOXが使用された．2012年1月26日，ロシュ社よりプライマリーエンドポイントであるOSにおける優越性が検証されたことがプレスリリースされた．同年の米国臨床腫瘍学会(ASCO)で詳細な結果が報告される予定であり，その内容が注目される．

実際の大腸がん治療レジメン

図6に，わが国の大腸癌治療ガイドライン示されている全身化学療法レジメンの治療アゴリズムを示す[2]．先述したように，BBPが検された状況で，今後のこのアルゴリズムがどように変わるのか，注視しておく必要があるこのアルゴリズムでも示されているが，現在広く実地臨床で用いられているベバシズマブ含むレジメンを図7,8に示した．すなわち，準的な大腸がん化学療法である，FOLFO XELOX(CapeOX)療法，FOLFIRI療法，sLV5FU療法にベバシズマブを加えた併用療法でありこれらは大腸がんの一次，二次化学療法として世界で汎用されているレジメンとなっている

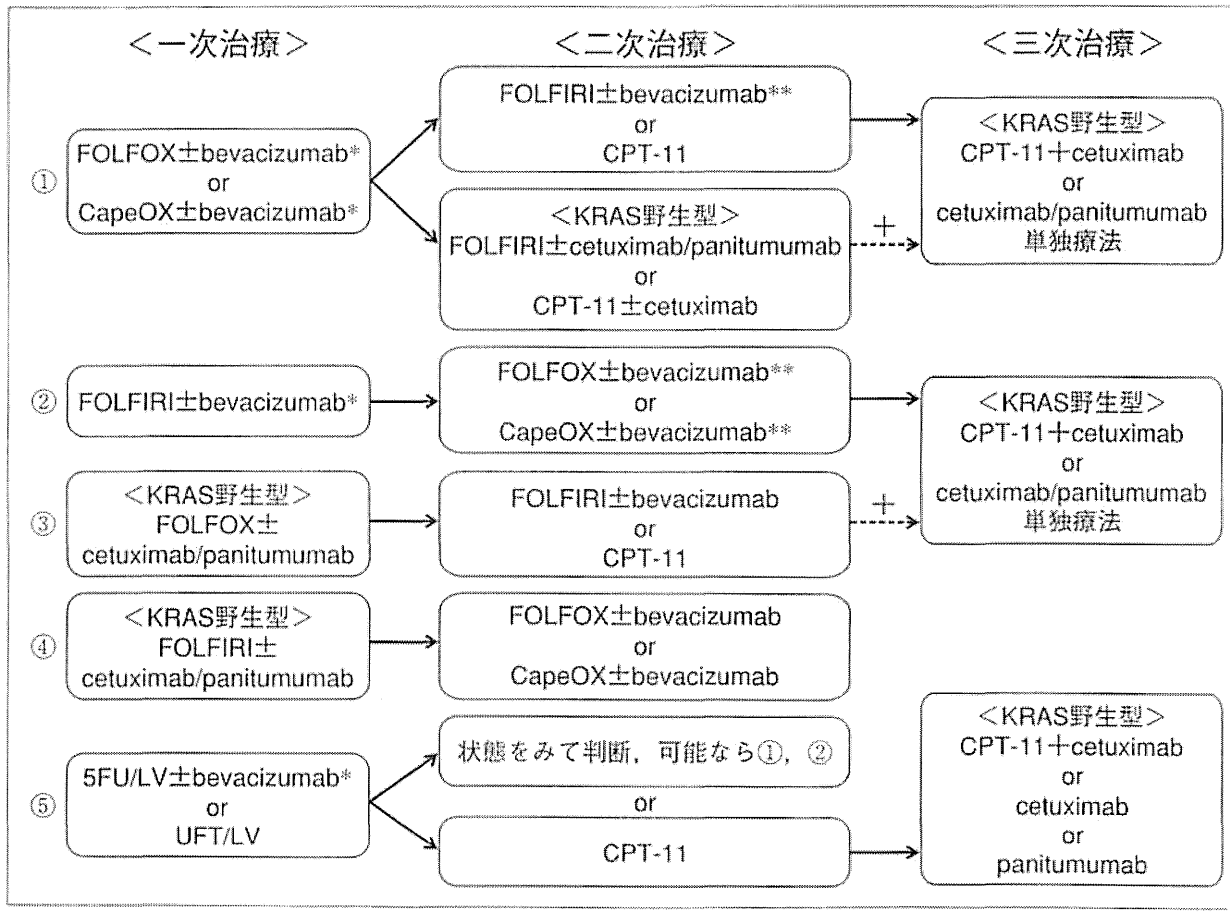

図6　大腸がんにおける全身化学療法のアルゴリズム

＊ベバシズマブの投与が推奨されるが，投与の適応でないと判断した場合はその限りではない．＊＊一次治療おいてベバシズマブを投与していない場合，および一次治療の効果が持続しているがCPT-11やL-OHPの毒性のめに投与を中止した場合は，二次治療でベバシズマブの投与が推奨される．＋：二次治療までに抗EGFR抗体を未使用の場合．

(大腸癌治療ガイドライン2010年改訂版より)

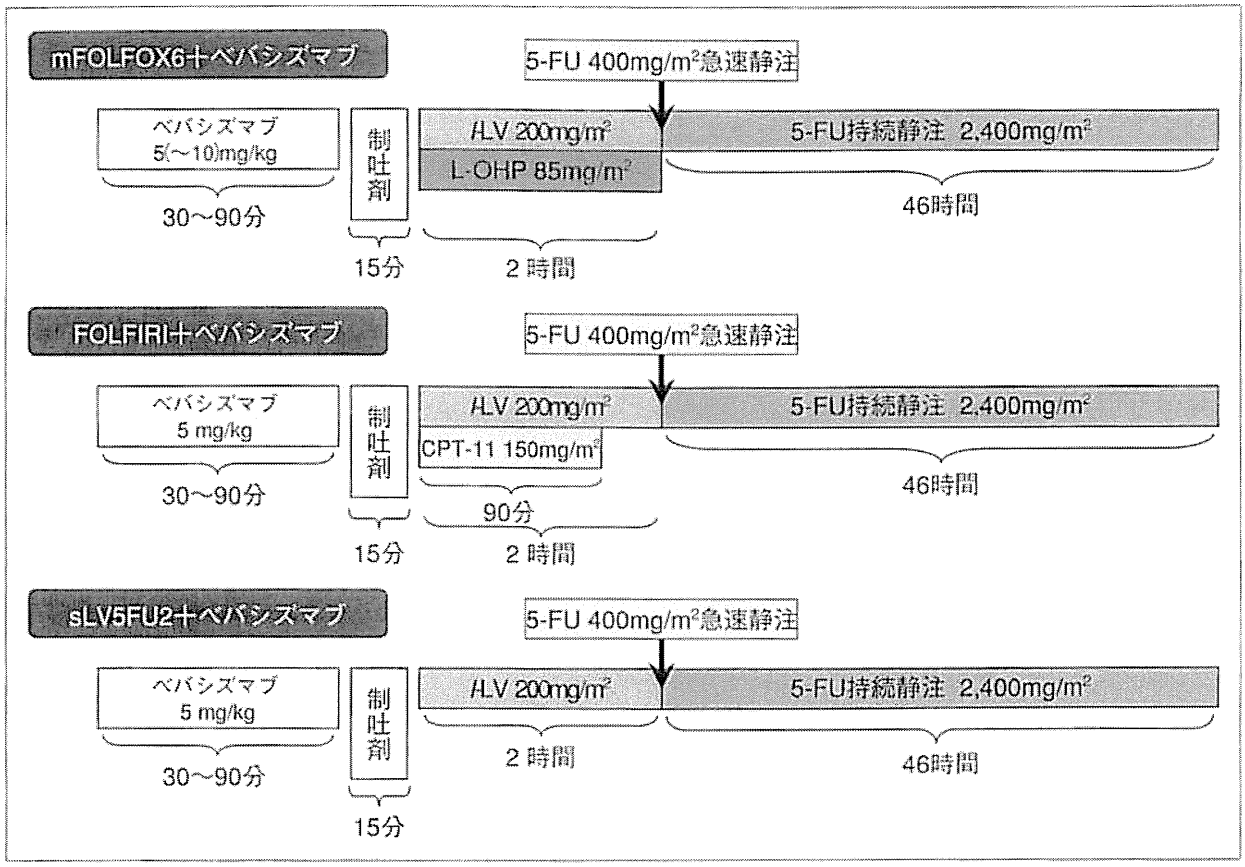

図7　各種抗がん剤(mFOLFOX6，FOLFIRI，sLV5FU2)とベバシズマブの併用療法

注意すべきベバシズマブ特有の副作用

ベバシズマブは特徴的な副作用を有するので，ほとんどが外来治療として行われている大腸がん治療において，注意すべき点も多い．まず，急性輸注反応(インフュージョンリアクション)は，抗体薬特有の副作用であり，蕁麻疹，呼吸困難，咽頭浮腫などに始まり，ショックやアナフィラキシー症状まで至ってしまうことが稀にある．発症時期に特定の傾向はないので，本剤投与時には常に頭の片隅にこの副作用を念頭に置き，発症時には迅速な対応が求められる．

また，動・静脈の血栓塞栓症や消化管穿孔は生命にかかわるものなのである．外来化学療法患者が本剤を投与している場合における突然の腹痛や四肢の浮腫，疼痛の出現など急変の際には，上記副作用を想定して，迅速な対応を講じる必要がある．同時に，日頃からの注意深い観察の必要と急変時における施設単位での対応マニュアルなどを構築しておくことが望ましい．Grade 1～2程度の軽度の高血圧や鼻出血などの軽微な出血は比較的高頻度に起こるが，重篤となる場合は少ない．

今後大腸がんで臨床導入が期待される血管新生阻害薬

2012年，American Society of Clinical Oncology-Gastrointestinal Tract Cancer(ASCO-GI)においてCORRECT試験の結果が報告され，レゴラフェニブの有用性が証明された．レゴラフェニブは経口マルチキナーゼ阻害剤であり低分子化合物である．血管新生にかかわる受容体型チロシンキナーゼ(VEGFR 1～3, TIE2)および間質系にかかわる受容体型チロシンキナーゼ(PDGFR-β, FGFR)，発がんに関与する受容体型チロシンキナーゼ(KIT, PDGFR, RET)に対する阻害作用を有する．CORRECT試験は，プライマリーエンドポイントをOSに置き，標準的化学療法に不応の切除不能進行・再発大腸がん(いわゆるサルベージライン)に対するレゴラフェニブの有用性を評価する多施設共同プラセボ対照二重盲検無作為化比較第III相国際共同試験である．本試験では

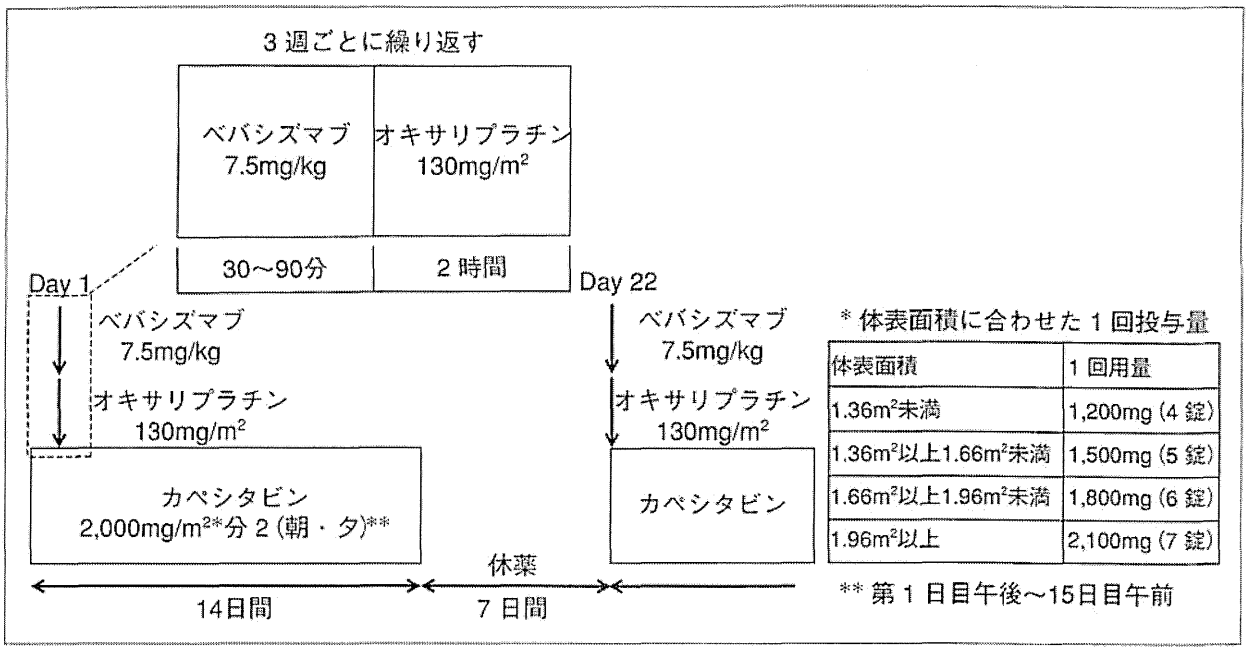

図8　XELOX(CapeOX)＋ベバシズマブ療法

日本からも100例の患者が短期間で登録され，症例集積に大きく貢献した点にも注目を集めた．これまでに，切除不能進行・再発大腸がんに対して，スニチニブ，ソラフェニブ，セジラニブなど多数の低分子化合物の開発がなされてきたが，OSの延長には結びつかなかった．多くの試験が初回(一次)化学療法における化学療法への上乗せ効果を検証するものであったが，マルチターゲットの低分子化合物の毒性が比較的強く多岐にわたることから，併用により従来の化学療法剤のdose intensityを下げてしまうことが問題となっていた．本剤は，大腸がんではじめて有効性を示した低分子化合物となったが，単剤でかつサルベージラインでの開発が成功に結びついた主要因であると考えられる．今後の承認，実臨床への応用に期待がかかる．

おわりに

大腸がん化学療法は，5-FU，イリノテカン，オキサリプラチンの抗がん剤とベバシズマブ，セツキシマブ，パニツムマブの分子標的治療薬の導入により明らかな生存期間の延長を獲得し，個別化治療の第一歩を踏み始めた．わが国は長らく欧米で構築されたエビデンスに追従せざるをえない状況であったが，ここにきて少なくとも薬剤環境に関してはようやく欧米並みになった．しかし，まだまだ日本全国のすべての医師が高度に複雑化した大腸がん化学療法を十分に使いこなせているわけではない．大腸がん領域におけるベバシズマブは，最も使用頻度の高い薬剤の一つになってきている．つまり，最も基本的な薬剤であり，今後ますます適正使用に心がけていく必要がある．

また，新たな血管新生阻害薬として，この1，2年で承認されるであろうレゴラフェニブではgrade 3以上の手足症候群，倦怠感，高血圧，下痢，皮疹が少なからず認められ，これらの毒性を適切にマネジメントする臨床力が求められる．どんな立場の医療者であろうとも，大腸がん化学療法に携わっている限り，up-to dateの知識の整理と最新の情報収集を怠らず行い，多くの臨床経験を積んでいくことが必要となる．適正な大腸がん化学療法を実践していくために，われわれ臨床家がなすべき課題はますます重く，多くなってきている．

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* * *

●原 著●

進行・再発大腸癌患者のmFOLFOX6およびFOLFIRI療法におけるパロノセトロンの制吐効果に関する後ろ向き調査

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〔*Jpn J Cancer Chemother* 39(8): 1215-1219, *August*, 2012〕

Antiemetic Effect of Palonosetron in Advanced Colorectal Cancer Patients Receiving mFOLFOX6 and FOLFIRI: A Retrospective Survey: Yumiko Sato[*1,5], Yuji Hayakawa[*2], Michiko Tatematsu[*3,5], Kei Muro[*4], Hidekazu Noma[*1] and Hirokazu Okamoto[*5] (*[*1]Dept. of Pharmacy, Nagoya City West Medical Center, [*2]Dept. of Pharmacy, Nagoya Medical Center, [*3]Dept. of Pharmacy, and [*4]Dept. of Clinical Oncology, Aichi Cancer Center Hospital, [*5]Graduate School of Pharmacy, Meijo University*)

Summary

Controlling chemotherapy-induced nausea and vomiting (CINV) is very important for the continuation of chemotherapy. CINV can significantly affect a patient's quality of life, leading to poor compliance with further chemotherapy treatment. In this retrospective study, we assessed the efficacy of palonosetron versus granisetron for the incidence of CINV induced by mFOLFOX6 and FOLFIRI in patients with advanced colorectal cancer. Eighty-eight patients were included in the efficacy analyses: 39 patients in the palonosetron group and 49 patients in the granisetron group. The incidence of nausea in the granisetron group (Grade 1: 40.8%, Grade 2: 10.2% and Grade 3: 4.1%) was significantly higher than in the palonosetron group (Grade 1: 25.6% and Grade 2: 7.7%, p=0.0422). The incidence of vomiting and appetite loss in the granisetron group was not significantly higher than in the palonosetron group (p=0.2419, p=0.2648, respectively). This suggests that palonosetron exerts better efficacy against chemotherapy-induced nausea than granisetron in patients receiving mFOLFOX6 and FOLFIRI. Information on such analyses is useful to promote the effectiveness of cancer chemotherapy. **Key words**: Chemotherapy-induced nausea and vomiting (CINV), FOLFIRI, mFOLFOX6, Palonosetron (*Received Sep. 22, 2011/Accepted Dec. 22, 2011*)

要旨 がん化学療法誘発性の悪心・嘔吐(CINV)は，患者の生活の質を大きく損ない治療のコンプライアンス低下を招くため，その予防はがん化学療法の継続において極めて重要である。今回われわれは，mFOLFOX6療法およびFOLFIRI療法が施行された進行・再発大腸癌患者におけるpalonosetron(Palo)とgranisetron(Gra)の悪心・嘔吐予防効果を後ろ向きに調査した。対象患者88例中，Palo群は39例，Gra群は49例であった。Gra群の悪心発現頻度(Grade 1: 40.8%, Grade 2: 10.2%, Grade 3: 4.1%)は，Palo群と比較して有意に高かった(Grade 1: 25.6%, Grade 2: 7.7%, p=0.0422)。嘔吐および食欲不振の発現頻度は有意な差がなかった(p=0.2419およびp=0.2648)。これらの結果より，mFOLFOX6療法およびFOLFIRI療法を施行する患者の悪心予防におけるGraに対するPaloの有効性が示唆され，今後のがん化学療法に対して有効性を高める情報が得られた。

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はじめに

悪心・嘔吐は，がん化学療法の副作用のなかでも高頻度に発現する症状の一つであり，患者の quality of life を大きく損なう。悪心・嘔吐発現のメカニズムの一つは，抗がん剤投与により小腸粘膜に存在するクロム親和性細胞から放出されたセロトニンが，求心性迷走神経に存在する 5-hydroxytryptamine-3 (5-HT_3) 受容体に結合し，その刺激が嘔吐中枢に伝わることによる。5-HT_3受容体拮抗剤 (5-HT_3RA) は，5-HT_3受容体に結合し，セロトニンの働きをブロックすることで効果を発揮する。がん化学療法誘発性の悪心・嘔吐 (chemotherapy-induced nausea and vomiting: CINV) 予防に対して標準的に用いられる薬剤の一つである。

CINV の予防に関して，American Society of Clinical Oncology (ASCO) や National Comprehensive Cancer Network (NCCN)，Multinational Association of Supportive Care in Cancer (MASCC) などの組織がガイドライン (GL) を作成している。これらの GL では，中等度催吐性リスクの薬剤 (moderate emetogenic chemotherapeutic agents: MEC) に対しては 5-HT_3RA と dexamethasone (Dexa)，高度催吐性リスクの薬剤 (high emetogenic chemotherapeutic agents: HEC) に対しては 5-HT_3RA，Dexa および aprepitant (Apre) の 3 剤を併用することが推奨され，その発現リスク別の支持療法も示されている[1-3]。

現在，日本で市販されている 5-HT_3RA には，granisetron (Gra)，ondansetron (Onda)，tropisetron および palonosetron (Palo) などがあげられる。このうち Palo は半減期が約 40 時間であり，他の 5-HT_3RA よりも著しく長く，5-HT_3受容体への結合親和性は約 100 倍高い[4]。NCCN の最新の GL (V1.2012) では，HEC と MEC に対して Palo を推奨すると改訂された。また，2010 年出版された日本癌治療学会 (Japanese Society of Clinical Oncology: JSCO) の制吐薬適正使用 GL[5] では，MEC に対する制吐療法としては 5-HT_3RA と Dexa が推奨されているが，患者リスクに応じて Palo または Apre の使用を考慮すると記載されている。このように，5-HT_3RA 間における Palo の位置付けが見直されつつあるが，日本国内において MEC に対する Palo の優位性を明確にした報告は現在までない。

そこで今回，MEC に分類されている薬剤について Palo の悪心・嘔吐予防効果を評価する目的で，進行・再発大腸癌患者において広く実施されている mFOLFOX6 療法および FOLFIRI 療法に着目し調査した。これらのレジメンはともに進行・再発大腸癌の一次治療および二次治療で用いられ，治療効果および悪心・嘔吐の発現頻度は同等であると報告[6-9]されている。これらのレジメンを実施した患者を対象に，診療記録を用いた後ろ向き調査にて検討を行ったところ，若干の知見を得たので報告する。

I．対象・方法

1．対象患者

愛知県がんセンター中央病院において，2009 年 6 月 1 日～2011 年 5 月 31 日までに mFOLFOX6 療法または FOLFIRI 療法を初回施行された進行・再発大腸癌患者のうち，制吐支持療法として Gra 3 mg と Dexa 6.6 mg または Palo 0.75 mg と Dexa 6.6 mg の前投薬を受けた患者を対象とした。ただし，オピオイド，ベンゾジアゼピン系薬剤，抗ヒスタミン薬，bevacizumab (BV) 以外の分子標的抗がん剤を併用していた患者は対象より除外した。なお，BV については催吐性リスクは最小であり[3]，副作用として悪心・嘔吐の報告はない[10]。また，FOLFIRI 療法や mFOLFOX6 療法類似の化学療法との併用にて悪心・嘔吐の発現頻度を高めるといった報告もない[11,12]ため，除外しなかった。本研究の実施に当たり，愛知県がんセンター倫理審査委員会の承認を得た (受付番号 3-26)。

2．調査方法

全対象症例の診療録 (医師記録，看護記録，薬剤管理指導記録) および処方・注射オーダリング情報より，年齢，性別，performance status (PS)，合併症，化学療法歴，前投薬以外の制吐剤処方の有無，悪心・嘔吐，食欲不振および便秘の発現状況を調査した。悪心・嘔吐，食欲不振および便秘に関しては，前回の化学療法後から今回の来院時までの発現について，医師および看護師により Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) に基づき Grade 評価された記録を抽出した。

3．悪心・嘔吐，食欲不振および便秘の発現状況の検討

悪心・嘔吐，食欲不振および便秘の発現状況を，前投薬が Gra 3 mg 群と Palo 0.75 mg 群に分けて比較した。さらに，悪心の発現状況とその他の因子の関連性を検討するため，性別，年齢，レジメン，Dexa 処方の有無についてサブグループ解析を行った。なお，年齢の 2 群比較については，全体の中央値であった 63 歳を基準とし，63 歳未満群および 63 歳以上群の 2 群に分けて比較検討した。

4．統計学的解析

Grade 評価を含めた悪心・嘔吐の発現頻度の比較には，

Table 1 Characteristics of patients

	All	Granisetron	Palonosetron
Number of patients	88	49	39
Gender			
Male/Female	48/40	24/25	24/15
Age			
Median	63	62	63
Range	28-82	28-78	37-82
Performance status			
0/1/2	42/43/3	22/25/2	20/18/1
Number of prior chemotherapy			
1/2/3/4/5	29/37/18/3/1	18/21/8/1/1	11/16/10/2/0
Chemotherapy regimen			
mFOLFOX6/FOLFIRI	52/36	29/20	23/16
Prescription of antiemetics			
Dexamethasone	37	13	24
Other	62	35	27
Dexamethasone+other	29	13	16

Table 2 Chemotherapy regimens

		Number of patients	
		Granisetron	Palonosetron
mFOLFOX6	L-OHP 85 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2,400 mg/m^2, every 2 weeks	11	6
mFOLFOX6+BV	L-OHP 85 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2,400 mg/m^2, BV 5 mg/kg, every 2 weeks	18	17
FOLFIRI	CPT-11 150 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2,400 mg/m^2, every 2 weeks	5	3
FOLFIRI+BV	CPT-11 150 mg/m^2, levofolinate 200 mg/m^2, 5-FU 400 mg/m^2, 5-FU 2,400 mg/m^2, BV 5 mg/kg, every 2 weeks	15	13

BV: bevacizumab, CPT-11: irinotecan, L-OHP: oxaliplatin

Table 3 Effects of granisetron or palonosetron on nausea, vomiting, appetite loss or constipation induced by mFOLFOX6 and FOLFIRI

	Grade 1/2/3		p value (Mann-Whitney's U-test)
	Granisetron (n=49) n (%)	Palonosetron (n=39) n (%)	
Nausea	20 (40.8)/5 (10.2)/2 (4.1)	10 (25.6)/3 (7.7)/0 (0.0)	0.0422
Vomiting	5 (10.2)/2 (4.1)/1 (2.0)	1 (2.6)/2 (5.1)/0 (0.0)	0.2419
Appetite loss	21 (42.9)/4 (8.2)/2 (4.1)	11 (28.2)/5 (12.8)/0 (0.0)	0.2648
Constipation	13 (26.5)/0 (0.0)/0 (0.0)	12 (30.8)/2 (5.1)/0 (0.0)	0.2834

Mann-Whitney's U-test を用い，$p<0.05$ の場合を有意とした。患者背景の比較および悪心の発現頻度とその他の因子の関連性の検討についてはロジスティック回帰分析を用い，$p<0.05$ の場合を有意とした。

II．結　果

1．患者背景

患者背景を Table 1 に示す。Gra 3 mg が前投薬された患者群と Palo 0.75 mg が前投薬された患者群との間で，抗がん剤投与後の Dexa 処方については Palo 群で有意に多かった（$p=0.001$）が，それ以外の患者背景に差は認められず，また特記すべき合併症もなかった。mFOLFOX6 療法および FOLFIRI 療法のレジメンについて Table 2 に示した。

2．悪心・嘔吐，食欲不振および便秘の発現状況

悪心・嘔吐，食欲不振および便秘の発現状況を Table 3 に示す。悪心の発現について，Gra 3 mg が前投薬された患者群では Grade 1 が 40.8%（20/49），Grade 2 が