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Alternate-day S-1 Oral Therapy for Frail Patients With Metastatic Colorectal and Pancreatic Cancer

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Abstract

Background/Aim: Standard therapies are difficult to implement in vulnerable patients. S-1 alternative daily therapy has been reported to be a low-burden drug therapy for metastatic colorectal cancer in elderly patients. The vulnerable elders survey-13 (VES-13) is a tool to identify vulnerable elderly patients. In this study, we investigated the utility of simultaneous and serial measurements of the VES-13 and cancer prognostic factors, neutrophil-to-lymphocyte ratio (NLR) and tumor markers (TM), during chemotherapy in patients receiving S-1 every other day.
Patients and Methods: We studied five patients with metastatic colorectal cancer and eight patients with pancreatic cancer who received S-1 on alternate days. The NLR, TM levels, and VES-13 scores were measured monthly before and during chemotherapy. A scatterplot of NLR on the horizontal axis and TM levels on the vertical axis was plotted together with the VES-13.
Results: The NLR and VES-13 scores showed a positive correlation, and both increased in cases of bowel obstruction or enteritis. Following the evaluation of progressive disease, two patients with colon cancer and two with pancreatic cancer were eligible to switch to the standard treatment regimen.
Conclusion: Alternate-day S-1 therapy appears to be a feasible and effective treatment option for frail patients with metastatic colorectal and pancreatic cancer. Continuous monitoring of the NLR and VES-13 scores can aid in the stratification of patients, ensuring that treatment intensity is appropriately matched to the patient's condition.

Keywords: Vulnerable elders survey-13, activities of daily living, neutrophil-to-lymphocyte ratio.

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Introduction

Guidelines for cancer treatment in older individuals recommend comprehensive geriatric assessment (CGA) for pharmacotherapy (1). However, CGA requires 1.5-2 h of evaluation, which is difficult to implement in daily practice. The vulnerable elders survey-13 (VES-13) is used to identify geriatric patients to alleviate these problems (2). It is a questionnaire-based assessment consisting of items addressing age, health status, and activities of daily living (ADL), with a score of ≥3 indicating vulnerability. The causes of reduced ADL in patients with recurrent cancer after surgery include primary age-related and secondary tumor and surgery-related functional decline.

No consensus on the definition of frailty exists, and using this term only in the older population is inappropriate. The prevalence of frailty increases with ageing (3, 4). Asakawa *et al.* broadly distinguish between "aging-related frailty" and "nonaging-related frailty," such as disease-related frailty. However, this distinction can be difficult (5). On the other hand, the "Colorectal Cancer Treatment Guidelines for Physicians 2019" define patients who are suitable for drug therapy as fit, those for which indication should be carefully assessed as vulnerable, and those who are not fit for drug therapy as frail according to the tolerability of standard drug therapy (6). Colorectal cancer guidelines also define the best supportive care for frail patients. If they are considered vulnerable, they may be able to tolerate less intense treatment and achieve at least some therapeutic effect. However, no clear measure distinguishes frail from vulnerable individuals. Gastrointestinal cancers are generally treated with cytotoxic anticancer drugs and molecularly targeted agents; however, few studies have investigated the administration of these agents in patients with a performance status (PS) of 3-4. Alternate-day S-1 treatment has been reported to be a less intensive drug therapy for older patients with multiple lung metastases of colorectal cancer (7). There is a report recommending the use of gemcitabine+nanoparticle albumin-based paclitaxel therapy (GEM+nabPTX) for Japanese patients with pancreatic cancer who are losing weight, but this report does not consider the use of S-1 (8). For Japanese patients with pancreatic cancer, S-1 administered every other day is a treatment with less toxicity than S-1 administered every day (9).

We investigated the feasibility of simultaneous and serial measurement of the neutrophil-to-lymphocyte ratio (NLR) and tumor marker (TM) levels using VES-13 during chemotherapy, including postoperative recurrence, in patients with colorectal and pancreatic cancer who underwent alternating-day treatment with S-1.

Patients and Methods

Patient selection. Five patients with metastatic colorectal cancer and eight with pancreatic cancer [66-90 years of age (median age, 73 years)] who had a VES-13 score >3 and were treated with S-1 on alternate days, between January 2013 and December 2018 at Niitsu Medical Center Hospital were included. Five patients experienced postoperative recurrence of colorectal cancer and five experienced postoperative recurrence of pancreatic cancer. Surgical procedures for colorectal cancer included primary resection in three patients, colostomy in one, and bypass in one; for pancreatic cancer, the surgical procedures included pylorus-preserving pancreaticoduodenectomy in two, Williamson's operation in two, and spleen-preserving pancreatectomy in one (Table I). The NLR, TM [CA19-9 and carcinoembryonic antigen (CEA)] levels, and VES-13 scores were measured monthly before and during chemotherapy (Table II). The score ranged 0-10, while a score ≥3 was considered indicative of impairment. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Niitsu Medical Center Hospital.

Regimen and treatment algorithm. The treatment consisted of alternate-day administration of S-1 (10). After confirmation of progressive disease (PD), patients were

Table I. *Patient characteristics.*

Case	Age	Sex	Primary site	Therapy			Post S-1 survival	Pre S-1 VES-13	PS	eGFR (ml/min)
				1st line	2nd line	3rd line				
1	78	Female	Colon	Ope	S-1	–	1M, dead	6	4	125
2	68	Male	Rectum	FOLFOX6 +Bmab	Radiation	S-1	8M, dead	6	2	104
3	81	Female	Colon	S-1	FOLFOX6 +Bmab	FOLFIRI +Pmab	8M, dead	8	3	53
4	66	Male	Rectum	Radiation	bypass	S-1	16M, alive	7	3	94
5	75	Male	Colon	S-1	Adhesiolysis	FOLFOX6	24M, dead	3	2	71
6	82	Male	Pb	S-1	–	–	6 M, dead	4	2	63
7	67	Male	Ph	Williamson	S-1	–	6 M, dead	6	3	91
8	68	Male	Pb	GEM+nabPTX	FOLFIRINOX	S-1	8 M, dead	3	2	92
9	90	Male	Pb	S-1	–	–	9 M, dead	10	3	70
10	71	Male	Pb	SPDP	S-1	GEM+nabPTX	14 M, alive	3	2	71
11	79	Female	Ph	PPPD	S-1	–	20 M, alive	8	3	58
12	71	Male	Ph	PPPD	S-1	GEM+nabPTX	26 M, alive	3	2	74
13	73	Male	Ph	Williamson	S-1	–	32 M, dead	3	2	96

VES-13: Vulnerable elders survey-13; PS: performance status; Ph: pancreatic head; Pb: pancreatic body; PPPD: pylorus-preserving pancreatoduodenectomy; SPDP: spleen-preserving distal pancreatectomy, GEM: gemcitabine; nabPTX: nanoparticle albumin-based paclitaxel; Bmab: bevacizumab; Pmab: panitumumab; FOLFOX6: leucovorin, fluorouracil, oxaliplatin; FOLFIRI: leucovorin, fluorouracil, irinotecan.

transferred to the standard regimen if the side effects were tolerable. The regimen was modified according to baseline PD (Figure 1).

Determination of tumor response and adverse events. Antitumor efficacy was determined based on computed tomography findings in accordance with the RECIST guidelines, version 1.17 (11). Toxicities during chemotherapy were graded according to the Common Terminology Criteria for CTCAE ver. 4.0.

Measurement of NLR, TM levels, and VES-13 score. The NLR, TM levels, and VES-13 score were measured before and during chemotherapy. The NLR was calculated as the ratio of the number of neutrophils and lymphocytes in the peripheral blood (12). A cross-graph (origin NLR, 2.5; CEA, 5) with NLR on the horizontal axis and TM (CEA) on the vertical axis was created (12). The graph depicts the monthly NLR and TM levels. The NLR and TM were plotted for each month and the transition of VES-13 was examined.

Table II. *Elements included in the vulnerable elders survey-13 (VES-13).*

Elements of assessment	Score
Age	
75-84	1
≥85	3
Self-Reported Health	
Good, very good or excellent	0
Fair or poor	1
ADLs/IADLs	
A lot of difficulty in:	
Stopping, crouching or kneeling	1
Lifting or carrying 10 lbs	1
Reaching or extending arm above shoulder	1
Walking a quarter of a mile	1
Doing heavy housework	1
	(Maximum of 2 points)
	4 points for one or more items
Activities	
Needs helps in:	
Shopping	
Managing money	
Doing light housework	
Walking across the room	
Bathing	

ADLs: Activities of daily living; IADLs: Instrumental Activities of Daily Living.

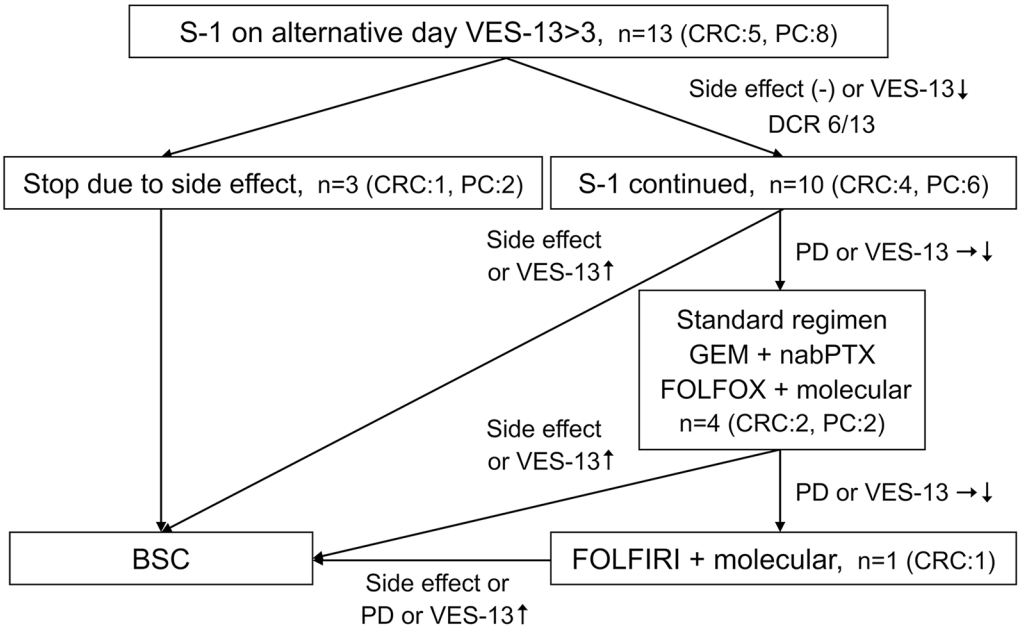

Figure 1. *Early discontinuation due to adverse events was observed in one case of colorectal cancer (Grade 3 diarrhea) and two cases of pancreatic cancer (Grade 2 anorexia, Grade 3 diarrhea). Two cases of colorectal cancer and two cases of pancreatic cancer (FOLFOX6, FOLFIRI + Pmab, GEM+nabPTX) were eligible for conversion from S-1 alternate-day treatment to standard therapy. DCR: Disease control rate; VES-13: vulnerable elders survey-13; CRC: colon cancer; PC: pancreatic cancer; PD: progressive disease: GEM: gemcitabine; nabPTX: nanoparticle albumin-based paclitaxel; molecular: molecular target drug; BSC: best supportive care.*

Statistical analysis. All statistical analyses were performed using EZR, a statistical software package that extends the functions of R and R Commander and is distributed free of charge on the website of the Saitama Medical Center, Jichi Medical University (Saitama, Japan). Spearman's correlation coefficient test was used (13).

Results

The duration of the alternate-day S-1 treatment ranged 1-32 months (median, 9 months). Before S-1 treatment, VES-13 score ranged from 3 to 10 (mean, 5.2; 5.6 for colorectal cancer; and 5 for pancreatic cancer), while eight (61%) and two (15%) patients experienced grade ≥2 and grade ≥3 adverse events, respectively; additionally, one patient (case 1) discontinued early due to adverse events related to colorectal cancer (grade 3 diarrhea, VES-13 score, 6 points), and two patients for adverse events related to pancreatic cancer (grade 2 anorexia, VES-13, 6 points). Two patients with pancreatic cancer (patients 9 and 11) had VES-13 scores of 8 and 10, respectively (Table I). The responses achieved with S-1 alternate-day administration were the following: 1 partial response (PR), 3 stable disease (SD), and 1 progressive disease (PD) for colorectal cancer, and 2 PR, 4 SD, and 2 PD for pancreatic cancer. Liver metastases exhibited PR in two of the five patients treated with S-1 after pancreatic cancer surgery. The NLR and VES-13 scores were positively correlated (correlation coefficient, 0.62), and both increased with intestinal obstruction and enteritis (Figure 2).

In a patient who received radiotherapy (Patients 4) and presented a vesicorectal fistula due to rectal cancer, bypass surgery was performed for bowel obstruction caused by radiation enteritis. S-1 was administered every other day after surgery, and the primary tumor was

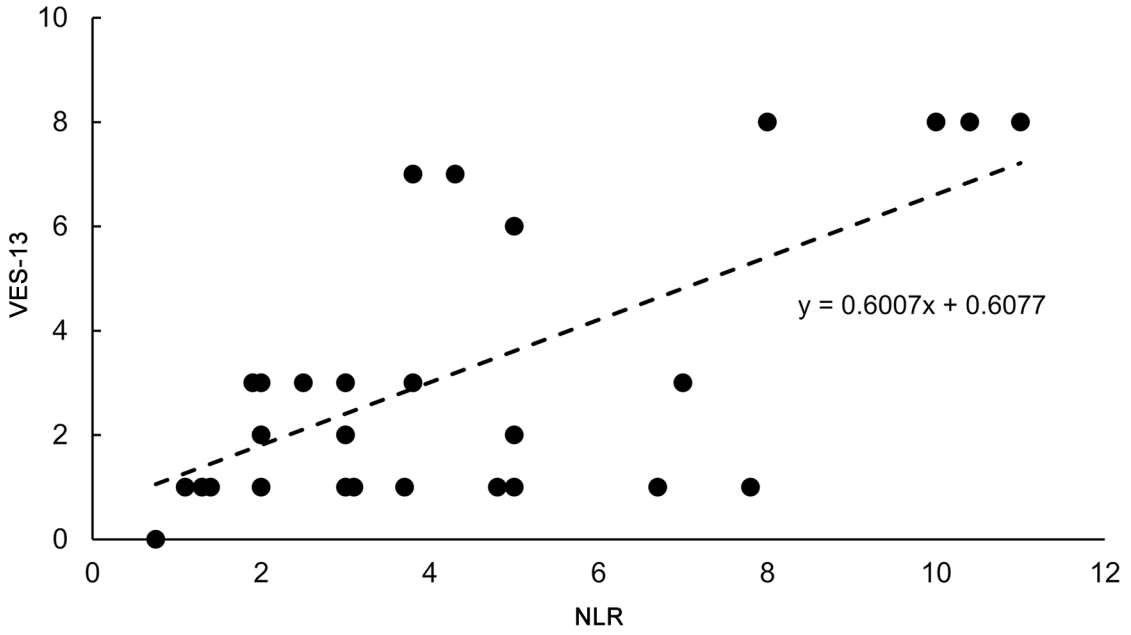

Figure 2. *Neutrophil-to-lymphocyte ratio (NLR) and vulnerable elders survey-13 (VES-13) are positively correlated (correlation coefficient, 0.62).*

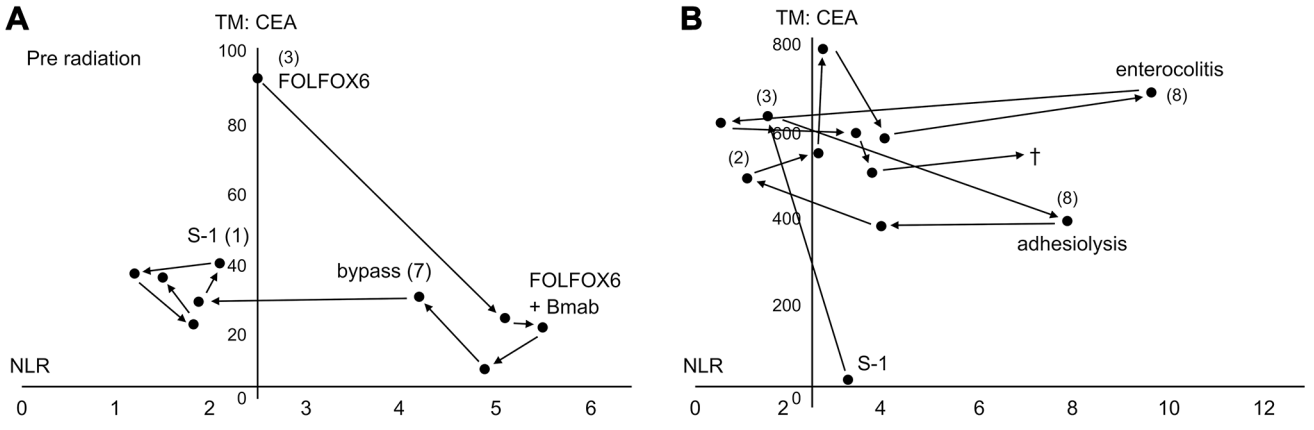

Figure 3. *A cross-graph [origin neutrophil-to-lymphocyte ratio (NLR), 2.5; carcinoembryonic antigen (CEA), 5] with NLR on the horizontal axis and tumor marker (TM) (CEA) on the vertical axis was created. The graph depicts monthly NLR and TM levels. The NLR and TM were plotted for each month and the transition of VES-13 was examined. VES-13 values are listed in parentheses. In case 4 (A), the patient had a bowel obstruction and underwent bypass surgery. At the onset of bowel obstruction, both NLR and VES-13 were elevated, but no further increase was observed in TM. Case 5 (B) was complicated by enterocolitis during chemotherapy without elevation of TM. Case 5 (B) showed a decrease in NLR and VES-13 after adhesiolysis. Bmab: Bevacizumab.*

controlled for 16 months using alternate S-1. At the onset of bowel obstruction, both the NLR and VES-13 score were elevated, but no further increase in TM levels was observed. Patient 5 presented similar complications with bowel obstruction and enterocolitis during chemotherapy; however, no elevation was observed in TM levels (Figure 3A). Patient 5 exhibited a decrease in the NLR and VES-13 score after adhesion debridement, and the treatment

regimen was changed to 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX6) (Figure 3B).

Discussion

Treatment guidelines for lung cancer recommend the administration of kinase inhibitors in patients with non-small cell lung cancer with positive driver gene mutations and PS 3-4 (14). However, few studies have investigated the treatment of gastrointestinal cancers in patients with PS 3-4, although treatment with molecular targeted agents in addition to cytotoxic anticancer agents is common.

After starting alternate-day administration of S-1, treatment was discontinued within 1 month due to adverse events in two patients with pancreatic cancer and one with colorectal cancer, both of whom had a high VES-13 score (≥6) before the start of treatment. In contrast, in the cases with an elevated NLR due to intestinal obstruction or enteritis without elevated TM levels (patients 4 and 5), the VES-13 score also increased to >7. However, as the intestinal obstruction improved with surgery or treatment, VES-13 decreased to <3, and the NLR to <2.5. Moreover, NLR and VES-13 score exhibited a positive correlation, reflecting the condition of the host.

The decline in ADL in older patients with cancer is a complex condition that includes a decline in host reserve due to aging in addition to a functional decline secondary to tumors and surgery (15, 16). Postoperative adjuvant chemotherapy, TM levels, NLR, and VES-13 score can be assessed during chemotherapy, therefore aid in determining whether fluctuations in ADL are tumor-derived, requiring appropriate treatment strategy.

After PD assessment, only two patients with colorectal cancer and two with pancreatic cancer were able to switch to the standard regimen; however, the modified standard regimens [FOLFOX6, 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) + panitumumab, and GEM + nabPTX] successfully achieved disease control.

Betge *et al.* reported that calculation of the CGA score and stratification of treatment for each treatment cycle could increase survival and reduce the use of inappropriate chemotherapy in unfit patients (17). Changes in the NLR before and three months after chemotherapy have been reported as a prognostic factor for colorectal cancer patients. Furthermore, the NLR can provide useful information for selecting treatment methods and may also lead to improvements in patient quality of life (18). In such cases, the treatment intensity increased when an improvement in the CGA score was observed. In our effective case, the NLR and VES-13 score decreased, while PS improved, suggesting that alternate-day S-1 treatment may be a potential tool to stratify patients for which determination of frailty or vulnerability is challenging. The incidence of grade ≥3 adverse events tended to be lower than that of conventional daily S-1, as reported by Yamaue *et al*., suggesting that alternate-day S-1 treatment may be a useful option for patients with impaired gastrointestinal and physiological function (10). However, the evidence was poor because of the retrospective nature of this study involving a small number of patients from a single institution. In this study, we used the VES-13 score, which mainly evaluates physical symptoms. However, in addition to the physical aspects of frailty in patients with cancer, various other factors, such as mental aspects and family environment, must be considered. Regarding the standard regimen, the treatment chosen in this study was based on 5-FU added to molecular targeted agents for colorectal cancer and gemcitabine for pancreatic cancer; however, this remains debatable. Currently, the individualization of chemotherapy for colorectal cancer is mainly based on tumor factors such as RAS mutations and left-right side differences in the primary site. The study highlights the potential of alternate-day S-1 therapy in stratifying frail and vulnerable patients. By continuously monitoring NLR and VES-13 scores, clinicians can better identify patients who may benefit from less intensive treatment while avoiding overtreatment and its associated risks. This approach is consistent with the growing emphasis on personalized medicine, where treatment is tailored to individual patient characteristics, including their physiological and functional status (19).

Conclusion

Alternate-day S-1 treatment may be useful for patients with colorectal and pancreatic cancer and impaired physiological function. In addition, continuous measurement of TM levels, NLR and VES-13 scores simultaneously helps to stratify patients and ensure that the intensity of treatment is appropriately matched to the patient's condition. These findings support the ongoing shift towards personalized cancer care, particularly in the elderly population with complex health needs.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

K.M. conceived and designed the study. N.O, J.K, and M.S. performed the experiments and wrote the manuscript. K.M. revised the manuscript. All the Authors approved the final version of the manuscript.

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