the physicians were specialists, and 42.0% were general practitioners (GPs). More than half (59.4%) practiced in community hospitals, 53.4% had cared for 10 or fewer patients in the past 6 months, and 50.2% used the WHO three-step ladder. Approximately 64.0% of physicians were not members of a palliative care team.

Knowledge regarding use of opioids for CPM

The mean knowledge score of the physicians and policy makers/regulators were 6.4 ± 2.6 and 4.8 ± 2.9, respectively. Table 2 shows that the lowest percentage of correct answers in both groups was with the item which indicated that physical dependence while on opioids is a sign of addiction (27.4% of the physicians and 19.1% of policy makers/regulators).

Figure 1 demonstrates that the majority of both groups had inadequate knowledge (62.1% of physicians and 74.5% of policy makers/regulators). To identify the associates of background characteristics with inadequate knowledge, further analysis was performed using univariate logistic regression. Table 3 shows that some background characteristics had significant associations with the knowledge level of physicians such as gender; age; last time of CPM education or training; medical specialty; hospital type; number of cancer patients being cared for in the past six months; use of the WHO three-step ladder; and membership in a palliative care team. Gender and last time of CPM education or training had significant effects among policy makers/regulators.

Table 2 Knowledge of participants regarding use of opioids for cancer pain management (CPM)

Items	Physicians (n=219)	Policy makers/Regulators (n=47)	*P* value [a]
	Correct answer N (%)	Correct answer N (%)	
1. Should use pethidine more than morphine in CPM. [b]	183 (83.6)	31 (66.0)	0.006
2. For long-term use, pethidine causes fewer adverse effects including tolerance and addiction. [b]	118 (53.9)	22 (46.8)	0.378
3. In chronic cancer pain, should not administer opioids on an "around-the-clock" basis. [b]	174 (79.5)	24 (51.1)	<0.001
4. Administering opioids in a PRN [d] dosing schedule can decrease the harmful effect of opioids such as tolerance, addiction or side effect. [b]	112 (51.1)	14 (29.8)	0.008
5. Parenteral administration is more effective than oral administration in pain management. [b]	110 (50.2)	12 (25.5)	0.002
6. Morphine is slowly and incompletely absorbed in the gastrointestinal tract. Patients should not take morphine by mouth even though they can eat food normally. [b]	167 (76.3)	31 (66.0)	0.142
7. The appropriate dose of morphine for cancer pain is whatever dose relieves the pain as completely as possible: there is no ceiling dose for morphine. [c]	125 (57.1)	18 (38.3)	0.019
8. Respiratory depression is serious but is rare when opioids are given at appropriate doses. [c]	130 (59.4)	15 (31.9)	0.001
9. Physical dependence while on opioids is a sign of addiction. [b]	60 (27.4)	9 (19.1)	0.242
10. At the present time, morphine oral solution dosage form is available at Food and Drug Administration, Thailand. [c]	143 (65.3)	27 (57.4)	0.319
11. Due to Narcotics Act B.E. [e] 2522 (1979), no limiting on doses and the number of days' supply that may be provided in a single prescription of category II opioids. [c]	71 (32.4)	22 (46.8)	0.061

[a] *P* value by Chi-square test; [b] Correct answer: "disagree" or "strongly disagree"; [c] Correct answer: "agree" or "strongly agree" [d] PRN (pro re nata) = as needed; [e] B.E. = Buddhist Era

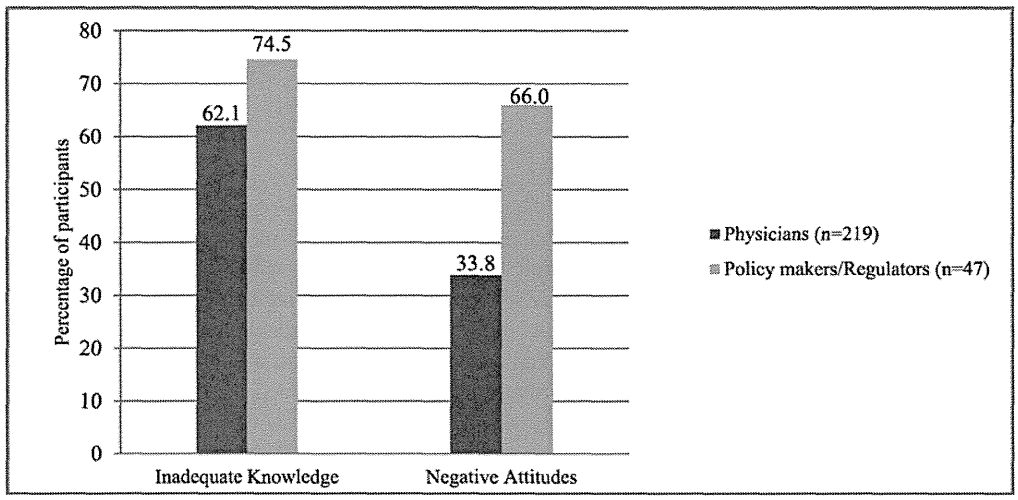

Fig. 1 Level of knowledge and attitudes of participants regarding use of opioids for cancer pain management

Table 3 Logistic regression analysis of related factors associated with inadequate knowledge regarding use of opioids for cancer pain management (CPM)

Variables	Knowledge of Physicians (n=219)				Knowledge of Policy makers/Regulators (n=47)			
	% Inadequate (n=136)	% Adequate (n =83)	OR[a] (95% CI[b])	*P* value	% Inadequate (n=35)	% Adequate (n=35)	OR[a] (95% CI[b])	*P* value
Gender								
Female	35.3	54.2	1 (Reference)		48.6	91.7	1 (Reference)	
Male	64.7	45.8	2.2 (1.2–3.8)	0.006	51.4	8.3	11.7 (1.4–100.2)	0.025
Age (y)								
≤ 35	55.9	41.0	1.8 (1.1–3.2)	0.033	31.4	33.3	0.9 (0.2–3.7)	0.903
≥ 36	44.1	59.0	1 (Reference)		68.6	66.7	1 (Reference)	
Last time in CPM education or training (y)								
< 1	4.4	28.9	1 (Reference)		5.7	33.3	1 (Reference)	
≥ 1	38.2	53.0	4.7 (1.8–12.6)	0.002	34.3	41.7	4.8 (0.7–35.2)	0.123
Never	57.4	18.1	20.8 (7.3–59.5)	<0.001	60.0	25.0	14.0 (1.7–112.6)	0.013
Medical specialty								
Board certificate: Oncology	1.5	13.3	1 (Reference)					
Anesthesiology	3.7	27.7	1.2 (0.2–7.2)	0.845				
Surgery	12.5	10.8	10.4 (1.9–57.4)	0.007				
Other	31.6	20.5	13.9 (2.8–69.5)	0.001				
General Practice[c]	50.7	27.7	16.5 (3.4–80.0)	0.001				
Hospital type								
Medical school hospital	0.7	7.2	1 (Reference)					
Community hospital	69.9	42.2	16.3 (1.9–140.1)	0.011				
General hospital	10.3	12.0	8.4 (0.9–81.1)	0.066				
Regional hospital	4.4	19.3	2.3 (0.2–22.8)	0.492				
Cancer center	1.5	4.8	3.0 (0.2–45.2)	0.427				
Other	13.2	14.5	9.0 (1.0–84.5)	0.054				
Number of cancer patients being cared for in the past 6 months								
≤ 10	63.2	37.3	6.8 (3.0–15.4)	<0.001				
11–30	28.7	30.1	3.8 (1.62–9.1)	0.002				
≥ 31	8.1	32.5	1 (Reference)					
Use of the World Health Organization (WHO) three-step ladder								
Yes	28.7	85.5	1 (Reference)					
No	29.4	4.8	18.2 (6.1–54.7)	<0.001				
Don't know the WHO three-step ladder	41.9	9.6	13.0 (5.6–30.0)	<0.001				
Be a member of the palliative care team								
Yes	23.5	56.6	1 (Reference)					
No	76.5	43.4	4.2 (2.4–7.6)	<0.001				

[a] OR: odds ratio; [b] CI: confidence interval; [c] General Practice: Reference group is oncology.

Table 4 Attitudes of participants regarding use of opioids for cancer pain management (CPM)

Items	Physicians (n=219)	Policy makers/ Regulators (n=47)	*P* value [a]
	Desirable answer N (%)	Desirable answer N (%)	
1. Only pain specialist should be responsible for the management of pain in cancer patients. [b]	202 (92.2)	14 (29.8)	<0.001
2. Use of opioids should be limited to patients with severe, intractable pain. [b]	69 (31.5)	12 (25.5)	0.419
3. Patients and their relatives should be informed that opioids are not good therefore they should put up with their pain as much as possible. [b]	182 (83.1)	32 (68.1)	0.018
4. Cancer patients should not receive opioids because of side effects. [b]	192 (87.7)	34 (72.3)	0.008
5. Cancer patients with pain no need to receive opioids because there are many other analgesics that we do not fear about diversion and abuse of opioids. [b]	113 (51.6)	22 (46.8)	0.551
6. Have a great deal of empathy for the patients with cancer pain so should provide sufficient opioids in Thailand. [c]	201 (91.8)	41 (87.2)	0.324
7. Hospital should have a stock of opioids. [c]	151 (68.9)	32 (68.1)	0.908
8. Physicians should not prescribe opioids chronically for cancer pain relief because it may have legal sanctions/ legal punishment. [b]	175 (79.9)	36 (76.6)	0.611

[a] *P* value by Chi-square test; [b] Desirable answer: "disagree" or "strongly disagree"; [c] Desirable answer: "agree" or "strongly agree"

Attitudes regarding use of opioids for CPM

The mean attitude scores of the physicians and policy makers/regulators were 5.9 ± 1.5 and 4.7 ± 2.1, respectively. Table 4 shows that the lowest percentage of desirable answers in both groups was with the item which indicated that the use of opioids should be limited to patients with severe or intractable pain (31.5% of the physicians and 25.5% of policy makers/regulators).

Figure 1 shows that about one-third (33.8%) of physicians had negative attitudes, whereas 66.0% of policy makers/regulators had negative attitudes. Table 5 presents some background characteristics which had significant effects on attitudes of physicians, such as their medical specialty; number of cancer patients being cared for in the past six months; and use of the WHO three-step ladder the last time in CPM education or training. These characteristics also had a significant effect on policy makers/regulators.

Barriers to Opioid Availability for CPM

The barriers are demonstrated in Table 6. The lack of education and training opportunities in CPM is the greatest barrier among physicians. For policy makers/regulators, perceived shortages or interruptions in opioid manufacture or distribution were the greatest barriers.

DISCUSSION

To our knowledge, this is the first study focusing on the knowledge and attitudes of physicians and policy makers/regulators regarding use of opioids for CPM, and of their perceptions concerning barriers to opioid availability in Thailand. The main findings were that physicians and

Table 5 Logistic regression analysis of related factors associated with negative attitudes regarding use of opioids for cancer pain management (CPM)

Variables	Attitudes of Physicians (n=219)				Attitudes of Policy makers/Regulators (n=47)			
	% Negative (N=74)	% Positive (N=145)	OR[a] (95% CI[b])	*P* value	% Negative (N=31)	% Positive (N=16)	OR[a] (95% CI[b])	*P* value
Gender								
Female	44.6	41.4	1 (Reference)		51.6	75.0	1 (Reference)	
Male	55.4	58.6	0.9 (0.5–1.5)	0.649	48.4	25.0	2.8 (0.7–10.7)	0.128
Age (y)								
≤ 35	58.1	46.2	1.6 (0.9–2.8)	0.097	32.3	31.3	1.0 (0.3–3.8)	0.944
≥ 36	41.9	53.8	1 (Reference)		67.7	68.8	1 (Reference)	
Last time in CPM education or training (y)								
< 1	13.5	13.8	1 (Reference)		3.2	31.3	1 (Reference)	
≥ 1	31.1	50.3	0.6 (0.3–1.5)	0.310	29.0	50.0	5.6 (0.5–58.9)	0.150
Never	55.4	35.9	1.6 (0.7–3.7)	0.301	67.7	18.8	35.0 (3.0–411.5)	0.005
Medical specialty								
Board certificate: Oncology	6.8	5.5	1 (Reference)		–	–	–	–
Anesthesiology	2.7	17.9	0.1 (0.0–0.8)	0.024	–	–	–	-
Surgery	8.1	13.8	0.5 (0.1–2.0)	0.319	–	–	–	–
Other	28.4	26.9	0.9 (0.3–3.0)	0.813	–	–	–	–
General Practice[c]	54.1	35.9	1.2 (0.4–4.1)	0.733	–	–	–	–
Hospital type								
Medical school hospital	1.4	4.1	1 (Reference)		–	–	–	–
Community hospital	63.5	57.2	3.4 (0.4–29.1)	0.264	–	–	–	–
General hospital	10.8	11.0	3.0 (0.3–29.4)	0.345	–	–	–	–
Regional hospital	12.2	9.0	4.2 (0.4–40.7)	0.221	–	–	–	–
Cancer center	0.0	4.1	0.0 (0.0)	0.999	–	–	–	–
Other	12.2	14.5	2.6 (0.3–24.6)	0.412	–	–	–	–
Number of cancer patients being cared for in the past 6 months								
≤ 10	63.5	48.3	1.0 (0.5–2.2)	0.939	–	–	–	–
11–30	16.2	35.9	0.4 (0.1–0.9)	0.024	–	–	–	–
≥ 31	20.3	15.9	1 (Reference)		–	–	–	–
Use of the World Health Organization (WHO) three-step ladder								
Yes	44.6	53.1	1 (Reference)		–	–	–	–
No	28.4	15.9	2.1 (1.0–4.4)	0.039	–	–	–	–
Don't know the WHO three-step ladder	27.0	31.0	1.0 (0.5–2.0)	0.915	–	–	–	–
Be a member of the palliative care team								
Yes	32.4	37.9	1 (Reference)		–	–	–	–
No	67.6	62.1	1.3 (0.7–2.3)	0.423	–	–	–	–

[a] OR: odds ratio; [b] CI: confidence interval; [c] General Practice: Reference group is oncology.

policy makers/regulators had inadequate knowledge and negative attitudes concerning the proper use of opioids, and that there exist several barriers to opioid availability.

This study showed that physicians were more knowledgeable than policy makers/regulators regarding knowledge questions about the use of opioids, except for one question about opioid regulations. In addition, policy makers/regulators had more negative attitudes than physicians in all attitude items. This may be because some policy makers are not healthcare professionals, such as the representatives from the Office of the Attorney General, the Ministry of Defense and the Royal Thai Police, and do not have background knowledge in medicine. They are more concerned about public security. The explanation for the knowledge deficit about opioid regulations among physicians is that medical school curricula rarely include instruction about opioid regulations.

The knowledge question with the most incorrect answers from both groups concerned definitions of addiction and physical dependence. This misconception was also found in a previous study in Canada (18% of physicians) and another study in the United States (almost 10% of state medical board members).[25,26] Terminological confusion can deter physicians from using opioids, and policy makers/regulators from setting appropriate regulatory policies.[27] It must be noted that only 65.3% of physicians knew that morphine in an oral solution dosage form is now available at the Thai FDA. Because the physicians did not know the up-to-date information, there

Table 6 Identified barriers to opioid availability for cancer pain management (CPM) as serious problems in Thailand

Items	Physicians (n=219)		Policy makers/ Regulators (n=47)		*P* value [a]
	N	(%)	N	(%)	
1. There is a lack of education and training opportunities in CPM for health care professionals.	66	(30.1)	19	(40.4)	0.170
2. There is a lack of education about CPM for health policy makers and drug regulators.	64	(29.2)	16	(34.0)	0.513
3. Hospital pharmacy stocks insufficient opioid analgesics.	55	(25.1)	16	(34.0)	0.209
4. Shortages or interruptions in opioid manufacture or distribution periodically.	52	(23.7)	28	(59.6)	<0.001
5. There is a lack of communication about the need for opioids for cancer pain between key groups including health care professionals, health policy makers, drug regulators, and drug manufacturers.	39	(17.8)	25	(53.2)	<0.001
6. Key decision makers are overly concerned about drug abuse, addiction, or diversion.	36	(16.4)	14	(29.8)	0.034
7. Opioids are available but not in the needed dosage forms.	35	(16.0)	12	(25.5)	0.119
8. Opioids are available but not the needed right ones.	32	(14.6)	14	(29.8)	0.013
9. Hospital director is overly concerned about drug abuse and diversion.	28	(12.8)	14	(29.8)	0.004
10. Opioid analgesic products are too expensive.	28	(12.8)	8	(17.0)	0.441
11. Physician has excessive concern about addiction and side effects of opioids.	27	(12.3)	15	(31.9)	0.001
12. There is a lack of regulatory provision made for emergency prescription of opioids for patients with an urgent need for relief of severe pain when a physician may not be able to attend to them.	22	(10.0)	10	(21.3)	0.032

[a] *P* value by Chi-square test

was a missed opportunity to treat some cancer patients who needed the morphine oral solution.

Many physicians in this study displayed significantly inadequate knowledge toward opioid pharmacology compared with physicians in the United States, whereas the results of this study were not much different from those of other Asian countries. For example, 57.1% of physicians in this study and 31% of South Korean physicians answered correctly that there is no ceiling effect for opioids, while 87% of physicians in the State of New Hampshire and 99% of physicians in the State of Minnesota answered correctly.[14,28,29] Additionally, 49.8% of physicians in this study and 66.2% of Taiwanese physicians did not know that the oral route is efficacious.[15] We can point out that some Asian countries still have inadequate medical education regarding the use of opioids; furthermore, Thailand has only a few pain clinics available where medical students can practice.

For the attitudes about opioid abuse and diversion, 32% of state medical board members in the United States in 2004 considered this issue as a serious problem, whereas 53.2% of policy makers/regulators in our study were concerned about it. Realizing that the narcotics problem has become one of the most serious problems in Thailand, policy makers/regulators in our country are now very concerned about this issue. In addition, physicians in this study avoided prescribing opioids because of the fear of diversion or abuse. In 2000, the WHO, in cooperation with the International Narcotics Control Board (INCB), recommended the concept of balance, meaning

that laws and regulations should be sufficient for preventing diversion and trafficking, but that they should not compromise access to opioids for genuine medical need.[30]

A great number of policy makers/regulators (70.2%) considered that only a pain specialist should be responsible for the management of pain in cancer patients, in contrast with physicians (7.8%). Unfortunately, Thailand has only a few pain specialists available. The great majority of cancer pain patients are treated by their physician in charge, who usually relies on a general practitioner.[19] Hence, it seems to be that physicians understand this situation more than policy makers/regulators. We also found that GPs were more likely to have inadequate knowledge and negative attitudes than physicians in other specialties. The significant effect of medical specialty on attitudes and knowledge about CPM was reported by various other studies.[12,15,28] Our results revealed that oncologists appeared more knowledgeable in comparison to others; however, there was no statistical difference between anesthesiologists and oncologists. On the other hand, anesthesiologists showed significantly more positive attitudes than oncologists. The explanation for these findings could be that both anesthesiologists and oncologists take care of many cancer patients. However, anesthesiologists focus on cancer pain while oncologists focus on tumor treatment.

Furthermore, this study found that patient volume was another variable that affected physicians' knowledge. This result was similar to that of the previous study in Taiwan in which physicians who treated more cancer patients were more likely to have adequate knowledge.[15] We also reasoned that physicians who worked in community hospitals were more likely to have inadequate knowledge than physicians in other types of hospitals, because their hospitals usually have fewer cancer patients.

We found that physicians who had received education or training more recently were more likely to have adequate knowledge. Yun *et al.* indicated that physicians who had received CPM training more recently were more likely to prescribe morphine for severe cancer pain.[23] Hence, it is necessary to update their knowledge. Interestingly, the physicians who did not use the WHO three-step ladder were more likely to have inadequate knowledge and negative attitudes. Kim *et al.* illustrated that the real usage of the WHO three-step ladder can help in obtaining better and more adequate CPM results.[28] Being a member of a palliative care team was significantly associated with inadequate knowledge but was not significantly associated with negative attitudes. Palliative care team physicians were less likely to have inadequate knowledge. A previous study showed that hospital palliative care teams can positively influence the knowledge and attitudes of physicians towards the use of opioids for CPM.[31]

Identifying barriers is crucial in the initial step to improve opioid availability. Our study revealed that the lack of education and training opportunities in CPM for health care professionals is the greatest barrier among physicians. About half of the physicians in our study were GPs who worked mainly in community hospitals, and therefore desired to obtain better CPM training opportunities. Policy makers/regulators considered that shortages or interruptions in opioid manufacture or distribution were the greatest barriers. The barriers differ among countries. For example, the inadequate availability of oral opioids was reported as a significant barrier in Serbia, and the complicated regulations and problems related to attitudes and knowledge regarding opioids for pain relief among professionals and the public were the major barriers in India.[32,33]

This study had some limitations. First, the sample size of the policy makers/regulators was too small. Therefore, other narcotics subcommittees should be included in future research. The second limitation was the selection bias that we created by allowing the director of each hospital to select which physician responds to the questionnaire.

In conclusion, this study suggests that there are inadequate knowledge and negative attitudes among physicians and policy makers/regulators regarding the use of opioids for CPM in Thailand.

Continuing education for physicians and setting up conferences for policy makers/regulators are needed. Special education and training should be addressed to clarify the terms "physical dependence" and "addiction." Basic knowledge updates regarding opioid pharmacology and narcotics laws are also needed, especially for physicians working in community hospitals. Their negative attitudes should be corrected. Cooperation among key cancer treatment stakeholders in overcoming the opioid availability barriers is also needed.

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TOBACCO INDUCED DISEASES

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Association of smoked and smokeless tobacco use with migraine: a hospital-based case–control study in Dhaka, Bangladesh

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Abstract

Background: Several studies in the past have reported inconclusive evidences on association of smoking and migraine. Nevertheless, no study so far reported association of smokeless tobacco with migraine. The objective of this study was to examine the association of smoked and smokeless tobacco use with migraine.

Methods: A hospital-based case–control study was conducted at the neurology outpatient department of a tertiary care hospital in Dhaka, Bangladesh. We enrolled 138 migraine cases diagnosed during March-September 2010 in neurology outpatient department, and 276 gender and age matched healthy controls from among their attendants. Diagnosis of migraine was based on the International Headache Society criteria. Use of smokeless tobacco and smoking (cigarette/bidi/hukka) were determined by an interviewer administered questionnaire.

Results: Among the cases, 52.9% were overall tobacco users; 24.6% were only smokers, 15.9% only smokeless tobacco users and 12.3% used both. The respective figures among controls were 14.5%, 7.2%, 6.9% and 0.4% (P <0.001 for all). The conditional logistic regression analysis found that migraine had higher odds of exposure to smoked tobacco use, smokeless tobacco use, and both compared to control after adjusting for confounding variables (alcohol drinking, insufficient sleep, mental stress, and number of family members); adjusted odds ratio (aOR) was 6.6 (95% confidence interval [CI] = 2.2-19.6, P = 0.001), 5.8 (95%CI = 1.9-17.4, P = 0.001), and 54.2 (95%CI = 4.3-684.4, P = 0.002), respectively. The aOR of cigarette/bidi/hukka smoking for different doses was 5.5 (95%CI = 1.2-24.8, P = 0.027) for 1–5 times per day, 6.3 (95%CI = 1.8-21.2, P = 0.003) for 6–10 times per day, and 6.7 (95%CI = 1.9-23.2, P = 0.003) for >10 times per day relative to non users.

Conclusions: Both smoked and smokeless tobaccos were found to be associated with migraine. There is a need to incorporate smokeless tobacco along with smoked tobacco into the anti-tobacco awareness programs to reduce the burden of migraine in Bangladesh.

Keywords: Migraine, Smoked tobacco, Smoking, Smokeless tobacco, Bangladesh

Introduction

Migraine (without aura) was defined as recurring headache disorder that manifest in the form of attack, last 4–72 hours, unilateral, have a pulsating quality, moderate to severe in intensity, aggravated by routine physical activity and are associated with nausea or vomiting, photophobia and phonophobia [1]. It is a chronic neurovascular condition which occurs up to 15% of adult population in the Western world [2]. The burden of this disease is huge, as during the episodic attack, 90% of them experienced moderate to severe pain, 75% had some sort of disability, and 35% were confined to bed [3,4]. It is regarded as the 20th leading cause of years lived with disability (YLDs) at global level and is the 9th leading cause of disability in women [1]. It is one of the most common forms among the headache disorders affecting the private, social and work life of those afflicted. Repeated headache attacks and constant fear of the next, damage family life, social life and employment. It is mostly

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affects people of working age, but does trouble children as well. There is a dearth in population-based studies with regard to the burden of migraine in Bangladesh. One study reported that migraine is responsible for 26% of all headaches in Bangladesh [5].

Stress, smoking, pattern of sleep, weather change, missing a meal, bright light, certain food and alcohol consumption have been reported as major triggers of migraine [6-8]. Several studies demonstrated the relationship between smoking and migraine with inconsistent results [2,7-15]. However, it has not been examined if smokeless tobacco, which is highly prevalent in South Asian countries [16], is associated with migraine or not. In this region, smoked tobacco includes cigarettes, bidi (hand-rolled cigarette), hukka (water pipe for consuming smoked tobacco), while smokeless tobacco includes dried tobacco (dried tobacco leaf with betel leaf), zarda (mixture of dried tobacco leaf, spices and vegetable dyes), and gul (tobacco powder). The use of smoked tobacco in Bangladesh is much higher in males (44.7%) than females (1.5%); however, smokeless tobacco use is almost similar in both males (26.4%) and females (27.9%) [17,18].

The purpose of this study was to examine the relationship of both smoking and smokeless tobacco with migraine using a hospital-based case–control study design in Dhaka, Bangladesh.

Methods

Cases

Cases were 138 clinically confirmed migraine patients attended the neurology outpatient department (OPD) of Bangabandhu Sheikh Mujib Medical University (BSMMU) - a tertiary care hospital in Dhaka. Bangladesh for follow-up visits between March and September 2010. Inclusion criteria were: (1) migraine without aura diagnosed according to the criteria of the International Headache Society (IHS) [19], and (2) not suffering from known case of psychiatric illness, hypertension, hypothyroidism, or irregular menstruation. Pregnant women were not included in the study.

Controls

Controls were 276 attendants of the cases. Two controls were matched to each case by gender and age (± 5 years). Inclusion criteria were: (1) family relative of the patient, (2) person without any history of migraine, (3) not suffering from psychiatric illness, hypertension, hypothyroidism, irregular menstruation, and (4) not pregnant.

Data collection

Patients/attendants aged 12 years or above were included in the study. Data were collected using an interviewer-administered semi-structured questionnaire which was developed after intensive literature review and consultation with experts. The questionnaire had three parts; socio-demographic characteristics, tobacco use, and other possible risk factors (insufficient sleep, alcohol use, and mental stress). It was piloted among 15 migraine patients and 15 controls and necessary amendments were made according to the responses and suggestions of the interviewers. The respondents those who consumed any form of tobacco (smoked or smokeless) almost regularly during at least for the last six months were considered as tobacco user. The respondents were asked whether they consumed any alcoholic drink in the last two weeks. Insufficient sleep was considered as sleeping less than eight hours per day [11]. Mental stress was assessed based on the subjective judgment of the respondents. Before data collection, informed written consent was taken from the respondents. Objectives, procedure, risks, and benefits of participation in the study were included in the informed consent sheet. The participants were ensured that participation was voluntary and they were free to withdraw themselves at any time without any unwanted consequences. Moreover, confidentiality of collected data was maintained using a code for each respondent. Privacy of the participants was also maintained during data collection by interviewing into a separate room. A female health care provider was present during the interview of female respondents. The study was reviewed and approved by the Ethical Review Committee of National Institute of Preventive and Social Medicine (NIPSOM), Dhaka.

Statistical analyses

Statistical analyses were performed with the Statistical Package for the Social Science, version 18.0 (SPSS, Chicago, IL, USA). Student's t test for continuous variables and the chi square test for categorical variables were used in the assessment of differences between the two groups when appropriate. All the statistical tests were two-tailed and P values <0.05 were considered as statistically significant. Exposure variables and confounders were screened for inclusion in an initial multivariable conditional logistic regression model. Candidate variables with P values <0.05 were included in the multivariable logistic regression model. Separate logistic regression models were built based on the type of tobacco use (nonusers, smokeless tobacco users, smokers) and frequency of tobacco use (without smokeless tobacco users).

Results

Comparative features of cases and controls are listed in Table 1. The ages of cases and controls were identical. Cases and controls were similar with regard to education, marital status, income, and occupational status, but the former group had larger family size. More cases were smokeless tobacco users and smokers compared to

Table 1 Comparative features of cases and controls

	Cases	Controls	*P* value
Age, mean (±SD), yrs	27.7 (8.9)	27.7 (8.9)	0.994
Gender			1.000
Male	46 (33.3)	92 (33.3)	
Female	92 (66.7)	184 (66.7)	
Marital status			0.943
Married	84 (60.9)	167 (60.5)	
Unmarried	54 (39.1)	109 (39.5)	
Years of schooling, mean (±SD), yrs	10.7 (4.9)	10.8 (4.7)	0.882
Occupational status			0.459
Unemployed	96 (69.6)	182 (65.9)	
Employed	42 (30.4)	94 (34.1)	
Number of family member, mean (±SD)	5.0 (1.4)	4.3 (1.2)	<0.001
Monthly household income, mean (±SD) in BDT	15275.3 (8382.0)	14420.2 (7066.7)	0.304
Tobacco use			<0.001
Non users	65 (47.1)	236 (85.5)	
Smoking only	34 (24.6)	20 (7.2)	
Smokeless tobacco only	22 (15.9)	19 (6.9)	
Both smoking and smokeless	17 (12.3)	1 (0.4)	
Smoked tobacco users			<0.001
Non user	87 (63.0)	255 (92.4)	
Cigarette	32 (23.2)	17 (6.2)	
Bidi	14 (10.1)	3 (1.1)	
Hukka	5 (3.6)	1 (0.4)	
Smokeless tobacco users*			<0.001
Non users	99 (71.7)	256 (92.8)	
Betel quid with tobacco leaf	37 (26.8)	20 (7.2)	
Zarda	35 (25.4)	16 (5.8)	
Gul	6 (4.3)	2 (0.7)	
Number of cigarette/bidi/hukka per day			<0.001
Non user	87 (63.0)	255 (92.4)	
1-5	8 (5.8)	5 (1.8)	
6-10	16 (11.6)	7 (2.5)	
>10	27 (19.6)	9 (3.3)	
Alcohol use	19 (13.8)	4 (1.4)	<0.001
Insufficient sleep	75 (54.3)	95 (34.4)	<0.001
Mental stress	93 (67.4)	89 (32.2)	<0.001

Data are mean (SD, standard deviation) or n (%).
Abbreviations: BDT, Bangladeshi Taka; 1 USD = 84 Taka.
* Simultaneous consumption of >1 type of tobacco is common among smokeless tobacco users in Bangladesh.

controls. Among the cases, 52.8% were overall tobacco users, 24.6% were only smokers, 15.9% only smokeless tobacco users, and 12.3% used both. The respective figures among controls were 14.5%, 7.2%, 6.9%, and 0.4% (P <0.001 for all). Alcohol drinking, insufficient sleep and mental stress were more prevalent among cases compared to controls.

The conditional logistic regression analysis found that migraine had higher odds of exposure to smoked tobacco use, smokeless tobacco use, and both compared to control

Table 2 Odds ratios for migraine by type of tobacco use

Tobacco use	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Non users	1	Ref	1	Ref
Smoked tobacco	13.3 (5.5-32.4)	<0.001	6.6 (2.2-19.6)	0.001
Smokeless tobacco	8.4 (3.3-21.3)	<0.001	5.8 (1.9-17.4)	0.001
Both Smoked tobacco and Smokeless tobacco	133.9 (15.6-1146.0)	<0.001	54.2 (4.3-684.4)	0.002

Abbreviations: OR, Odds ratio, adjusted for alcohol use, insufficient sleep, mental stress and number of family member; CI, Confidence interval.

after adjusting for confounding variables (alcohol drinking, insufficient sleep, mental stress, and number of family members); adjusted odds ratio (aOR) was 6.6 (95% confidence interval [CI] = 2.2-19.6, $P = 0.001$), 5.8 (95% CI = 1.9-17.4, $P = 0.001$), and 54.2 (95%CI = 4.3-684.4, $P = 0.002$), respectively as shown in Table 2. The aOR of cigarette/bidi/hukka smoking for different doses was 5.5 (95%CI = 1.2-24.8, $P = 0.027$) for 1–5 times per day, 6.3 (95%CI = 1.8-21.2, $P = 0.003$) for 6–10 times per day, and 6.7 (95%CI = 1.9-23.2, $P = 0.003$) for >10 times per day relative to non users (Table 3).

Discussion

To our knowledge, this is the first study to examine the association between smokeless tobacco use and migraine headache. We observed that smokeless tobacco users also had comparable odds of developing migraine like that of smokers within the limits inherent in case–control studies. Our findings that odds of smokers for migraine are higher compared to controls have been already reported [9,10,12-15]. Our study adds smokeless tobacco use to the list of risk factors for migraine headaches. Together, these studies provide evidence that both smokeless tobacco users and smokers are more likely to develop migraine headache compared to their counterparts.

Review of the literature showed that the associations between smoking and migraine headaches are not consistent [2,7-15]. Our finding of strong association between migraine and smoking is in agreement with some studies [2,9,10,12-15], although several studies did not find any association between them [7,8,11]. One large descriptive study also reported some sort of relationship between smoking and migraine [20]. Chen et al. [20], based on 508 migraine cases and 3192 controls, observed that there were more smokers in migraine group compared to non-migraine group. This variation between the findings could be due to the difference in study design, sample size and study population. For example, Nazari et al. study [7] conducted among women only where smoking is rarely practiced in female gender. Fernandez-de-las-penas et al.'s study [11] did not follow the IHS classification for migraine diagnosis. Takeshima et al. study [8], on the other hand, was based on secondary data which was not primarily designed to examine the association between smoking and migraine headache. Our findings showed that there were some sort of dose–response relationship between frequency of smoking and migraine. Odds ratio of migraine headache increased among smokers with the increase in frequency of smoking per day. This feature is consistent with the findings reported by Lopez-Mesonero et al. [6] and Tietjen et al. [14].

Smokeless tobacco use is widely prevalent in South Asian countries [21]. In Bangladesh, among females, 94.7% of current tobacco users used only smokeless tobacco [17]. Like other South Asian countries, the traditional values do not widely permit women to smoke cigarettes. However, there is no such taboo against using smokeless tobacco [22]. Younger people hesitate to smoke in front of their elders; they never smoke in the presence of their parents and seniors. Smokeless tobacco is an exception. Chewing betel quid (betel leaf) with sliced betel nut and dried tobacco leaf is considered as a normal social behavior. Besides, these are considered as a symbol of hospitality in the rural areas. Even the poor would feel embarrassed if these were not offered to a guest [23]. It is a social custom to serve guests by betel quid and dried tobacco product after meal in a family or social event. As smokeless tobacco contains several hazardous compounds like that of smoked tobacco, awareness against this harmful habit is must to prevent tobacco-related health conditions [24]. Campaigns against all kinds of tobacco use involving doctors, local health

Table 3 Odds ratios for migraine by frequency of smoked tobacco use

Number of cigarette/bidi/hukka per day	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Non user	1	Ref	1	Ref
1-5	5.5 (1.4-21.1)	0.013	5.5 (1.2-24.8)	0.027
6-10	18.0 (6.4-50.8)	<0.001	6.3 (1.8-21.2)	0.003
>10	8.1 (2.9-22.7)	<0.001	6.7 (1.9-23.2)	0.003

Abbreviations: OR, Odds ratio, adjusted for alcohol use, insufficient sleep, mental stress and number of family member; CI, Confidence interval.

care workers, medicine shop keepers, barefoot doctors, and local community leaders could be more effective than other strategies. Health hazards warnings, along with nicotine and tar level, should be labeled on packets of dried tobacco leaf. Anti-tobacco campaigns by public agencies and mass media should also include smokeless tobacco in their agenda. Any efforts to reduce the use of smokeless tobacco will not only reduce migraine but also other chronic conditions [20].

Our study has several strengths which include IHS defined migraine (without aura) diagnosis, and selection of cases and controls from the same population. Although, we were aware about the issue of careful selection of controls and we have chosen controls with no past and present history of migraine attack, possibility of significant effect measures could not be eliminated. This was the major limitation of our study. Others limitations include: 1) Since our study was a prevalent case–control study, the ORs did not exactly demonstrate the relative risk of migraine incidence, but the association with those who visited the hospital a various length of period after the first pain attack. The cases with repeated pain and longer history were likely to be sampled. 2) Our study is subject to recall bias due to its study design. 3) Our findings may have limited generalizability as our study was based on a tertiary hospital. 4) Despite multivariable adjustment technique, there could be additional potential confounders which we could not measure. 5) Unavailability of dose–response data regarding smokeless tobacco was an important shortcoming in our study. 6) We couldn't measure mental stress by using any standard scale. 7) Finally, this prevalent case–control study prevents our ability to establish causal relationships or pathways to migraine headache as we do not know whether outcome was preceded by exposure or not. Further larger scale cohort study is needed to establish the association between tobacco consumption, specially smokeless tobacco and migraine.

Conclusions

This study indicated that both smoking and smokeless tobaccos were associated with migraine headache, although there were several limitations. As use of smokeless tobacco is widely prevalent in Bangladesh and has become a cultural norm especially in rural area, a multi-pronged approach involving community leaders, mass media, and anti-tobacco organizations is needed to formulate tobacco use cessation program along with smoked tobacco to reduce the burden of migraine in Bangladesh.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MABS contributed in the study design, data collection, and initial draft of the manuscript. MR carried out the statistical analyses and thoroughly revised the initial draft. MHOR performed study design and statistical analyses and revised the manuscript. SH was especially involved in the migraine section and study design. HK performed risk factors related to migraine section and draft of the manuscript. JS did extensive review of the study design, statistical analyses and helped to finalize the manuscript. NH carried out final revision of the manuscript. All authors read and approved the final manuscript.

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PHASE II STUDIES

Phase II clinical study of modified FOLFOX7 (intermittent oxaliplatin administration) plus bevacizumab in patients with unresectable metastatic colorectal cancer—CRAFT study

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Summary *Purpose* Continuous treatment with FOLFOX therapy is associated with peripheral nerve toxicity, and to improve this inconvenient side effect various methods of administration are being investigated. A regimen of intermittent oxaliplatin administration by continuous infusion therapy, i.e., modified FOLFOX7 (mFOLFOX7) + bevacizumab, was designed with the goal of alleviating severe peripheral nerve disorders and hematological toxicity. A phase II clinical study was conducted to evaluate the efficacy and safety of this regimen. *Methods* Previously untreated patients were assigned to mFOLFOX7 (oxaliplatin 85 mg/m^2, levofolinate [*l*-LV] 200 mg/m^2, 5-fluorouracil [5-FU] 2400 mg/m^2) + bevacizumab (5 mg/kg) administered every 2 weeks for 8 cycles, maintenance without oxaliplatin for 8 cycles, and reintroduction of mFOLFOX7 + bevacizumab for 8 cycles or until disease progression. Progression free survival (PFS) following the first dose (PFS 1) and following reintroduction of oxaliplatin (PFS 2) were used as indices for assessing the efficacy of intermittent administration. *Results* Fifty-two patients were enrolled, with median age of 64 years (range, 36–74). Median PFS 1 was 11.8 months (95 % confidence interval [CI], 9.5 to 13.7), median time to treatment failure was 10.3 months (95 % CI, 5.6 to 12.1), percentage of patients with neutropenia of grade 3 or higher was 7.8 %, and percentage with peripheral nerve disorders was 3.9 %. Response rate was 50 %, and 84.4 % of patients who started modified simplified LV5FU2 + bevacizumab were reintroduced to oxaliplatin. *Conclusion* By excluding 5-FU bolus administration and administering bevacizumab continuously the mFOLFOX7 + bevacizumab regimen with preplanned withdrawal of oxaliplatin showed high tolerability and prevented severe peripheral neuropathy and neutropenia without reducing efficacy.

Keywords Oxaliplatin · Bevacizumab · Stop-and-go · Modified FOLFOX7 · Metastatic colorectal cancer

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Introduction

In the 1980s, 5-fluorouracil (5-FU)/leucovorin (LV) was the standard recommended first-line therapy for unresectable

metastatic colorectal cancer (mCRC) [1, 2]. Since then, irinotecan and oxaliplatin have been developed, and 5-FU/LV/oxaliplatin (FOLFOX) [3–5] and 5-FU/LV/irinotecan (FOLFIRI) [6] are now recommended in the NCCN Guidelines in addition to 5-FU/LV therapy. Hurwitz et al. reported prolonged survival by combining bevacizumab with irinotecan plus bolus 5-FU (IFL) [7], and combinations of chemotherapy with several molecular targeting agents are now currently recommended in the NCCN Guidelines and in the guidelines from other countries. Prolonged survival as an additive effect of molecular targeting agents has been reported in first-line therapy with 5-FU/LV plus bevacizumab [8], and the additive effect of bevacizumab to an oxaliplatin-based regimen was demonstrated in the NO16966 study [9].

As described above, 5-FU/LV plus bevacizumab and FOLFOX plus bevacizumab have become established as standard, first-line therapies for unresectable mCRC. However, peripheral neuropathy and serious hematological toxicity, which are cumulative toxicities of oxaliplatin in FOLFOX, have been obstacles to continuous therapy [10]. To address this issue, oxaliplatin withdrawal (the stop-and-go concept) was systematically incorporated into the OPTIMOX1 study [11] and the OPTIMOX2 study [12] and was shown to be useful. Subsequently, a randomized phase III clinical study of bevacizumab combined with FOLFOX (the CONcePT trial) was conducted in order to validate the stop-and-go concept and to examine the incidence of peripheral neuropathy depending on the administration of calcium gluconate and magnesium sulfate (Ca/Mg formulation), with results reported at the American Society of Clinical Oncology Annual Meeting in 2008 [13]. In that study, continuous administration of oxaliplatin (continuous oxaliplatin; CO) and intermittent administration of oxaliplatin (intermittent oxaliplatin; IO) were compared using modified FOLFOX7 (mFOLFOX7; oxaliplatin 85 mg/m^2) plus bevacizumab. Median time to treatment failure (TTF), the primary endpoint, was 4.2 months in the CO arm and 5.6 months in the IO arm (HR, 0.58; P=0.0025), demonstrating that the IO arm was significantly better. The incidence of peripheral neuropathy of grade 3 or higher, the rate of discontinuation of therapy due to peripheral neuropathy, and the need to delay the treatment and/or reduce dose were all lower in the IO arm. That report suggested the oxaliplatin stop-and-go concept to be favorable even when bevacizumab was combined with FOLFOX, but it has not been established as the standard of care, and the clinical question of reintroducing oxaliplatin remains.

Therefore, we conducted the phase II CRAFT (Confirmation of Avastin and intermittent mFOLFOX7 Therapy in advanced colorectal cancer) study in order to examine the efficacy and safety of a regimen of mFOLFOX7 plus bevacizumab with intermittent oxaliplatin administration for Japanese colorectal cancer patients.

Materials and methods

This study was a multicenter phase II clinical study to examine the efficacy and safety of intermittent oxaliplatin administration in mFOLFOX7 plus bevacizumab as the first-line therapy for patients with unresectable colorectal cancer. The primary endpoint was progression-free survival 1 (PFS 1, the period from the start of the treatment to the point of first progression); secondary endpoints were time to treatment failure (TTF), response rate 1 (RR 1, the response rate during the first oxaliplatin treatment), progression-free survival 2 (PFS 2, the period from the first progression during maintenance to the second progression after reintroduction of oxaliplatin), response rate 2 (RR 2, the response rate during reintroduction of oxaliplatin following the first progression), and the safety.

Patient eligibility

Patients were entered into the study if they fulfilled the following inclusion criteria: 1) colorectal cancer was definitely diagnosed histologically; 2) the colorectal cancer was unresectable and metastatic; 3) the disease had not been treated with chemotherapy or radiation therapy; 4) at least one lesion was evaluable; 5) age 20 to 79 years; 6) the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was 0 or 1; and 7) they had sufficient bone-marrow, liver, and kidney functions. Patients were excluded if there was 1) suspicion of brain metastasis; 2) suspicion of arterial thromboembolism; 3) chronic inflammatory disease such as rheumatoid arthritis; 4) bleeding tendencies; 5) uncontrollable peptic ulcer, hypertension, diarrhea, or infection; 6) heart disease with symptoms; or 7) pregnancy or lactation.

This study was conducted in accordance with the World Medical Association Declaration of Helsinki and the Ethical Guidelines for Clinical Studies. The scientific and ethical validity of this study was reviewed by the Ethical Review Board of each participating facility, and the study was conducted after receiving their approval. Informed consent was obtained from all enrolled patients in writing before enrollment. This study was registered with UMIN-CTR (number: UMIN000002354).

Treatment plan and evaluation

The protocol treatment was started within 14 days after enrollment of patients who were determined to be eligible. On day 1, bevacizumab 5 mg/kg was administered by initial 90-min intravenous infusion (which could be shortened to 60 min at the second time and to 30 min from the third time), then oxaliplatin 85 mg/m^2 and levofolinate (*l*-LV) 200 mg/m^2 were administered by 120-min intravenous

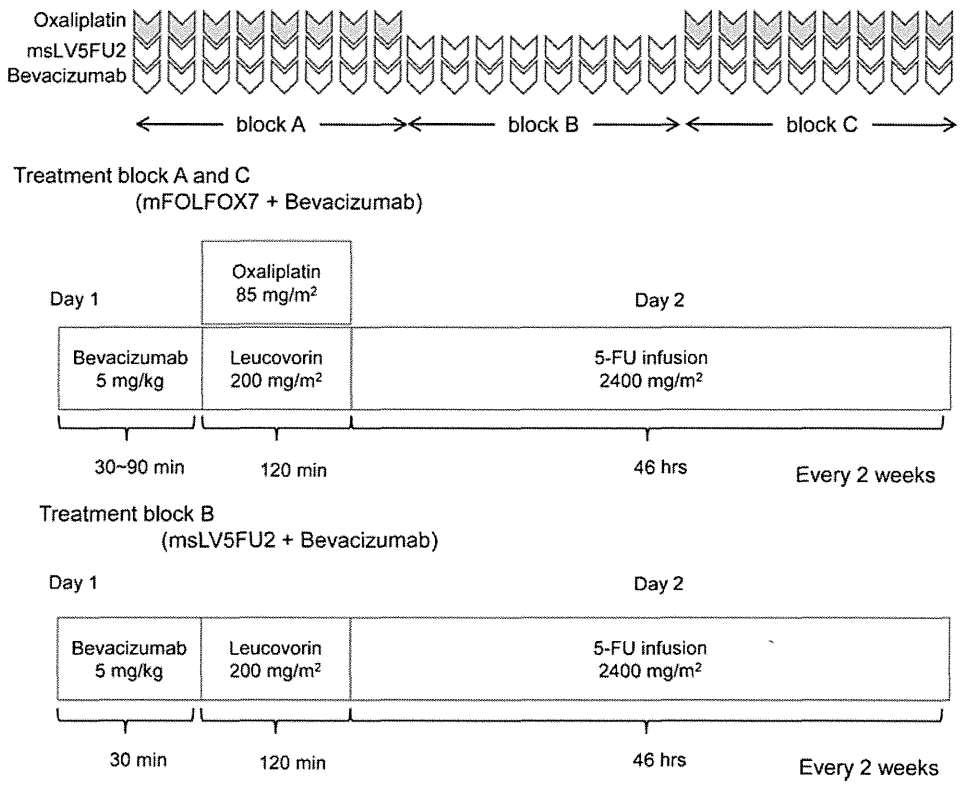


Fig. 1 Chemotherapy regimens

infusion, 5-FU 2400 mg/m^2 was administered by 46-h (days 1–2) continuous intravenous infusion, with 12 days of drug withdrawal thereafter. These 14 days constituted 1 cycle, and cycles 1–8 were conducted (block A). Thereafter, 8 cycles (cycles 9–16) were conducted without oxaliplatin (block B). Then oxaliplatin was reintroduced for 8 cycles (block C), so that a total of 24 cycles was administered as the protocol treatment (Fig. 1). Protocol treatment was continued as long as it did not conflict with the criteria for discontinuing treatment. However, the following cases were defined as the end of protocol treatment:

(1) The 24 cycles (block A followed by block B and then block C) prescribed in the protocol had been completed. However, if progressive disease (PD) was confirmed before the completion of 8 cycles in block B, the end of protocol was defined as the end of block C following reintroduction of oxaliplatin.
(2) The patient became operable as a result of the efficacy of treatment (with the day of surgery defined as the end of protocol treatment).

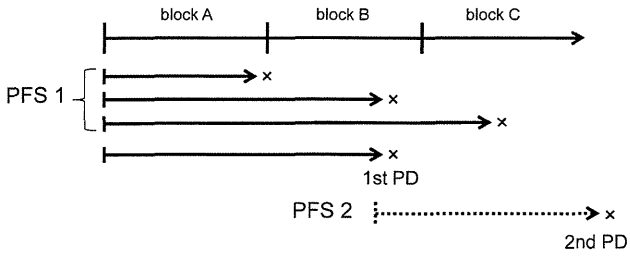


Fig. 2 Definition of progression free survival. PFS 2: first PD designated as starting point

Computerized tomography (CT)/magnetic resonance imaging (MRI) was performed every 8 weeks during the protocol treatment, counting from the day of enrollment, in order to measure and evaluate target lesions, evaluate non-target lesions, and check for the appearance of new lesions. Image assessment by CT/MRI or other method was also permitted as necessary. If the tumor site was measured by a method other than CT/MRI, the tumor was evaluated before treatment and the same method was continued until PD. As a rule, CT/MRI was also conducted using the same measurement method and the same slice thickness as used in examination at baseline. Evaluation of tumor reduction was according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).

Adverse events were evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v3.0) in all enrolled patients who received the protocol treatment at least once. The frequency and grade of the most serious clinical findings and laboratory test values in each cycle were tabulated. Patients were observed carefully for previously reported typical adverse drug reactions to bevacizumab and oxaliplatin, including hemorrhage,

Table 1 Baseline patient characteristics

Characteristics	*n*
Enrolled	52
Sex	
Male	32
Female	20
Age, years median (range)	64 (36–74)
ECOG performance status	
0	43
1	9
Primary site	
Colon	25
Rectum	27
Histological type	
tub1	5
tub2	36
por	5
muc	1
sig	2
ecc	1
Miscellaneous carcinoma	2
Site of metastasis	
Liver	34
Lung	21
Lymph node	12
Peritoneum	5
Surgery	
Yes	26
No	26

ECOG Eastern Cooperative Oncology Group
tub1 well differentiated type tubular adenocarcinoma
tub2 moderately differentiated type tubular adenocarcinoma
por poorly differentiated adenocarcinoma
muc mucinous adenocarcinoma
sig signet-ring cell carcinoma
ecc endocrine cell carcinoma

thrombosis, gastrointestinal perforation, increased blood pressure, hemotoxicity, and peripheral neuropathy.

Definition of endpoints

In this study, the following definitions were used to assess therapeutic effect: PFS 1 (Fig. 2) is the period from the day of enrollment to the confirmation of PD or death from any cause, whichever comes first; TTF is the period from the day of enrollment until the date of discontinuation of treatment, the date of PD confirmation, or the date of death, whichever comes first; RR 1 is the percentage of patients whose best overall response is either CR or PR; PFS 2 (Fig. 2) is the period from the date of first PD during modified simplified LV5FU2 (msLV5FU2) plus bevacizumab to the date of confirmation of PD (second PD after the day of enrollment) after reintroduction of mFOLFOX7 plus bevacizumab, or the date of death from any cause is confirmed, whichever comes first; RR 2 is the response rate during reintroduction of oxaliplatin following the first PD.

Statistical determination of target sample size

In the NO16966 study [9], a phase III clinical study of FOLFOX4 or capecitabine/oxaliplatin (XELOX) with/without bevacizumab, the median PFS by on-treatment analysis excluding PD cases from at least 29 days after the final administration of the study drug was 10.4 months. In the PACCE trial [14], a phase III clinical study conducted to confirm the additive effect of panitumumab to FOLFOX plus bevacizumab, the median PFS for FOLFOX plus bevacizumab was 11.2 months. Therefore, the threshold PFS in this study was assumed to be 7 months considering PFS in the phase III study of FOLFOX4 [15], and the anticipated PFS was set at 10.5 months. Level of significance was 0.05, power was 80 %, and the required number of cases determined by using the Southwest Oncology Group's one-arm survival design (http://www.swogstat.org/statoolsout.html) was 42 patients. The target number of cases in this study was 50 patients, considering a dropout rate of 10 %.

Analysis plan

PFS and TTF survival curves were estimated by the Kaplan–Meier method, median survival time was calculated, and the two-sided 95 % confidence interval was calculated.

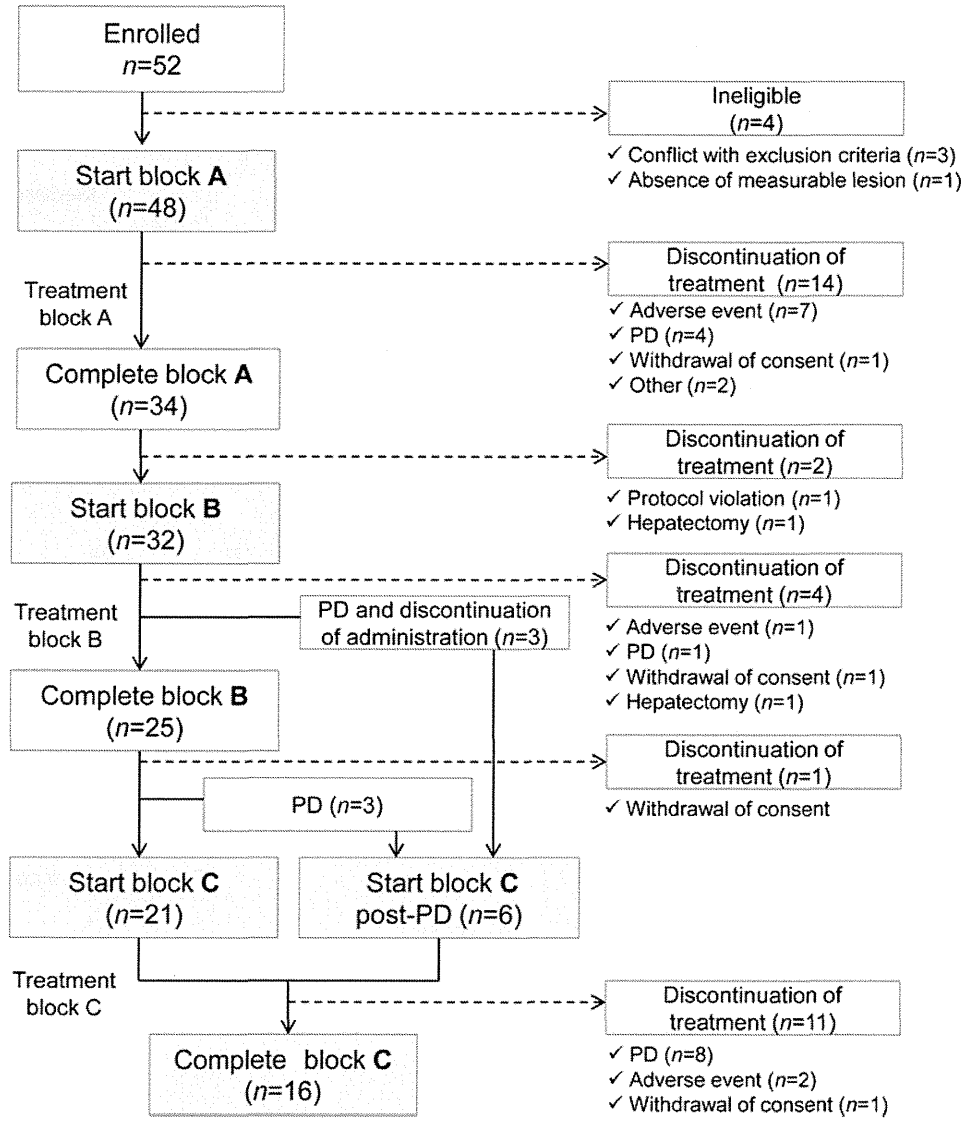
As for the response rate, antitumor effect (overall effect) was compiled for patients with measurable lesions among the per protocol set (PPS). Exact confidence interval based on binomial distribution was used for the interval estimation.

Results

Patient characteristics

Fifty-two patients from 18 institutions were enrolled from February 2009 to June 2010. Four out of the 52 patients were excluded as subjects of the efficacy analysis due to ineligibility after enrollment; therefore, the efficacy analysis was conducted with 48 patients. The safety analysis set included 51 patients, all enrolled patients who received the protocol treatment at least once. Data cutoff was May 2011, and the median observation period was 9.3 months. Baseline patient

Fig. 3 Study profile



characteristics are shown in Table 1. Median age was 64 years (36–74), male/female ratio was 32/20, colon cancer/rectal cancer ratio was 25/27, and ECOG PS 0/1 ratio was 43/9.

Treatment status

The study profile of protocol treatment is shown in Fig. 3. Of the 52 patients enrolled, 48 started the protocol treatment. The completion rate of block A treatment was 70.8 % (34/48). The breakdown of the 14 patients who discontinued treatment during block A was adverse events in 7 cases, PD in 4 cases, withdrawal of consent in 1 case, and other reasons in 2 cases. In addition, 1 patient deviated from protocol by continuing the treatment, and 1 patient discontinued due to hepatectomy after completing block A.

The rate of completion of block B treatment was 78.1 % (25/32). The breakdown of the seven patients who discontinued treatment during block B was PD in four cases, adverse event in one case, withdrawal of consent in one case, and hepatectomy in one case. A total of six patients with confirmed PD—three who discontinued block B and three who completed block B—were moved to block C as stipulated in the protocol. In addition, one patient discontinued due to withdrawal of consent after completing block B.

The rate of completion of block C treatment was 59.3 % (16/27). The breakdown of the 11 patients who discontinued treatment during block C was PD in eight cases, adverse events in two cases, and withdrawal of consent in one case.

The protocol completion rate was 33.3 % (16/48), and median TTF was 10.3 months (95 % confidence interval [CI], 5.6 to 12.1) (Fig. 4a).

The percentage of patients reintroduced to oxaliplatin at movement from block B to block C was 84.4 % (27/32).

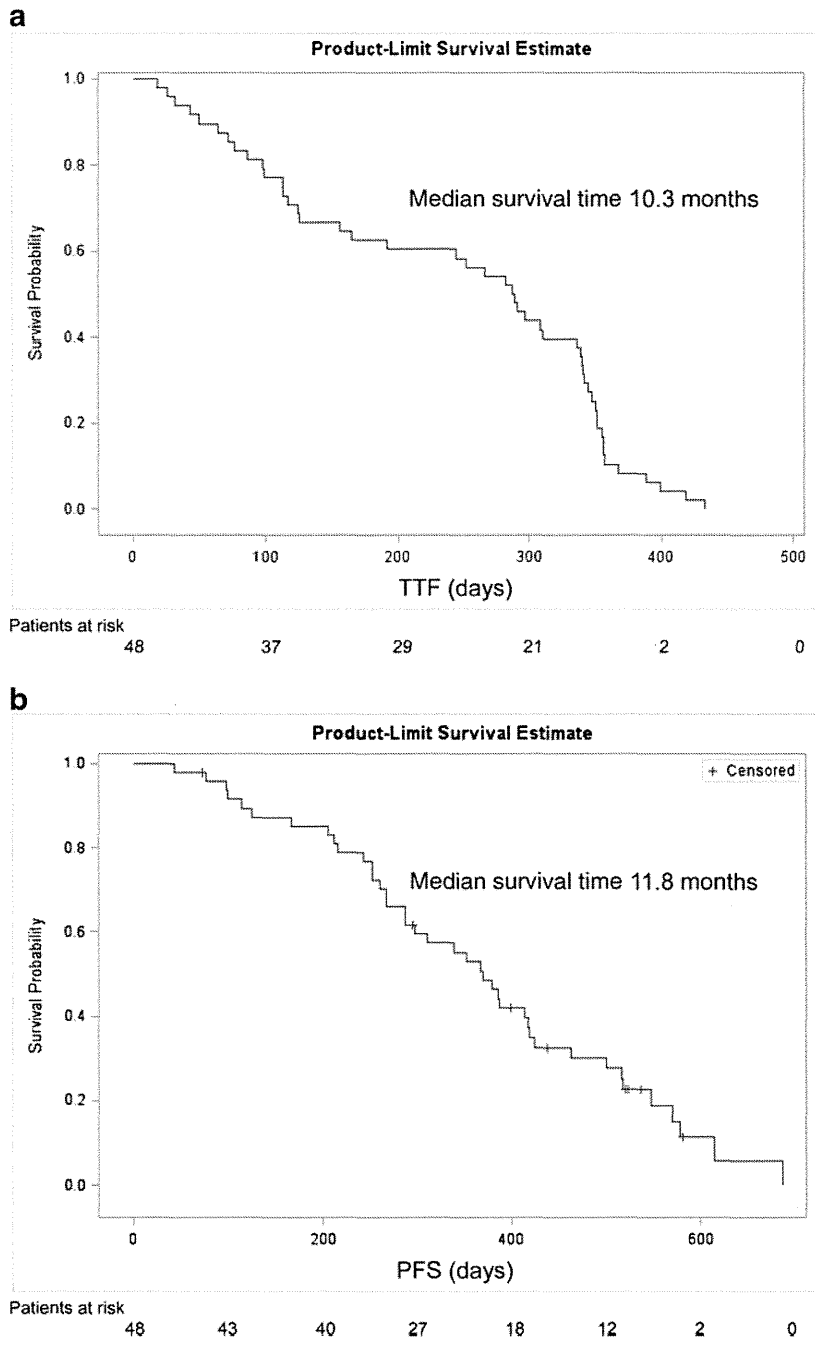


Fig. 4 **a** Kaplan-Meier estimate of time to treatment failure. **b** Kaplan-Meier estimate of progression free survival

Relative dose intensity in each treatment block was ≥89 % for 5-FU and *l*-LV, ≥86 % for bevacizumab, and ≥96 % for oxaliplatin (blocks A and C).

Efficacy

The median PFS 1, was 11.8 months (95 % CI, 9.5 to 13.7) (Fig. 4b). The secondary endpoint RR 1 was 50 % (23/46) in the 46 patients who were evaluable by RECIST. The maximum rate of tumor reduction at the time of best overall response during the protocol treatment was −91 % (range, +126.0 to −91.0 %). There were six patients to whom PFS 2 and RR 2 were applicable after oxaliplatin reintroduction as patients with first PD during or immediately after block B treatment. The median PFS 2 and RR 2 were 4.2 months (95 % CI, 2.8 to 23.5) and 0 % (0/6), with three cases of stable disease (SD) and three cases of PD. Exploratory analysis showed median survival time to be 25.4 months (95 % CI, 18.5 to 35.2).