HPAI[12]. Various activities, such as advocacy, workshops, and training of health staffs, community people, village health volunteers (VHVs), chiefs of villages, chiefs of communes, students of high schools, and junior high schools have been made in order to create awareness about HPAI, and to reduce exposure to the disease, particularly to stop endemic of HPAI in Cambodia. Information, education, and communication (IEC) materials, such as T-shirts, caps, posters, panoramas, leaflets, booklets, and calendars have been produced and distributed to Cambodian people not only in the affected areas, but also in other areas over the country. To harmonize avian and human influenza (AHI) materials, a Bird Flu IEC Committee was established in 2005, and then the AHI campaign started[13]. Moreover, the Communicable Disease Control Program initiated strategy to broadcast information necessary to prevent HPAI via mass media, like television (8 broadcasting a day for a month, once in 3 months), radio (10 times/2 minutes, 30 days/3 months), newspaper *etc*. Direct campaign by local staffs and villagers to the communities, especially during the main festival-days in every year also were conducted regularly.

From February 2005, the number of HPAI in human has spread in 5 provinces, such as Kampot, Kampong Cham, Kampong Speu, Prey Veng, and Kandal with 10 positive cases confirmed by Pasteur Institute of Cambodia located in Phnom Penh, Cambodia[12]. In addition, regular quarterly meetings have been conducted with local health workers in the communities around Kampot province in order to strengthen AI surveillance, and reporting health information system on infectious diseases.

According to the report of Cambodia Communities out of Crisis, 80.5% of Cambodians live in rural areas; 35% of the total population live with the income of $ 0.45 per person per day, below the national poverty line of $ 1 per person per day[14] and Cambodian's census in 2008 indicated that 47.2% of people over 25 years old were not primary completed and 13.4% were illiterate[15]. Rate of illiteracy was significantly higher among females than males. As there is no definitive treatment of HPAI and spread from poultry-to-poultry and poultry-to-human is common, it is crucial to raise awareness about HPAI among the most vulnerable population. Accordingly, we aimed to assess level of knowledge, attitudes, and practices (KAPs) among married women in Kampot province. As most of the household chores including handling of poultry are women-centered, it is crucial to assess and upgrade their level of KAPs regarding transmission, symptoms, treatment and prevention of HPAI. An effective strategy based on their level of KAP can efficiently help prevent HPAI among Cambodian population. Married women are particularly vulnerable and at high risk for severe complication of HPAI during interpandemic periods, in case of such pandemic due to emergence of HPAI viruses, because they take main responsibilities of housework such as raising poultry, food preparation, and taking care of their children[16]. Although published reports are available about HPAI-related KAPs, no such studies have ever reported on married women in Cambodia. Therefore, this study aimed at determining KAPs and its influential factors towards HPAI among Cambodian women. This baseline information about their awareness about HPAI could help policy makers and future researchers for effective planning and implementation.

2. Materials and methods

2.1. Study sites

The study was conducted in Kampot Operational District located in Kampot Province, Southern part of Cambodia, a typical area occupied by poor people of two different religions including Buddhism and Muslim. The study area located from 6 to 35 km to the Kampot town with population of 144 090 out of 585 110, the total population of Kampot province[15].

2.2. Study population

Two hundred and forty-six married women aged 18-55 years were enrolled in this cross-sectional study. Women who were residing in the village for at least one year before the survey were included; because, they had the opportunity to attend in various activities that have been done so far and to obtain information on HPAI from it. Included women were involved in many household works which threatened them to be in contact with HPAI, such as house keeping, taking care of their children, cooking food for the family members, educating their children, raising poultry, selling poultry, cleaning outdoor, and indoor around their houses. Legally eligible age for marriage of women in Cambodia is 18 years, so 18 years were the lower limit[17], and women aged over 55 years were the upper limit because this is the retiring age in Cambodia[18]. Women without having backyard poultry were also excluded from the study.

2.3. Survey methodologies

Trained health staff was responsible for collecting data with the help of the chiefs of the villages through face-to-face interview. Accordingly, both health staff and the village chiefs were trained about how to conduct the interview. Although, only the health staff were responsible for collecting data, the village chiefs were cooperating with them in identifying households and introducing the interviewers with them. Using a structured questionnaire, data was collected during November to December, 2009. Targeted sample of 300 eligible women were chosen through a multi-stage cluster sampling from the Kampot OD[19-22]. Initially, 5 communes were randomly chosen from 19 communes (of 21 communes in Kampot OD, 2 were excluded because they were located in the town). Fourteen villages were randomly selected from a total of 28 villages of the chosen communes. All the villages had similar number of eligible women and therefore, each village was treated as one Primary Sampling Unit (PSU). From each PSU, we selected 22 women systematically to get a total of 300 targeted women[23,24]. Only one woman was interviewed from each household. Lists of women were provided by the chief of each village. Because of their unwillingness to participate in the study, absence from home, we could interview 270 women. During data cleaning, 24 respondents were excluded because of incomplete information to make a final total of 246 women.

The questionnaire was developed with little modification

of the previously published questionnaire[21, 22, 25, 26]. Some new additional questions were created by local team. The questionnaire was designed in four sections: Section A contains demographic information; section B focuses on knowledge on AI which composed of 32 questions; Section C describes the prevention practices from HPAI which set with 20 questions, and Section D mentions on attitude related to HPAI which contains 11questions[20,23,24,27].

We set each section with one correct answer for each question. Those who answered correctly were scored 1 and 0 was scored for the wrong answers. The total scores of correct answers for each respondent were split at the mean because they were normally distributed data. Accordingly, level of knowledge on HPAI was categorized into "good" and "poor". If the correct answers were equal or more than the mean scores, the woman's knowledge was considered "good". If the correct answers were less than the mean, the woman's knowledge was considered "poor"[20,22,27,28]. Attitude was considered 'positive' for equal or more than mean score and 'negative'for score less than the mean. Same techniques were applied to categorized practices of the respondents into "good" (equal or more than mean score) and "bad" (less than mean score)[20,25]. Questionnaire was translated into local language, validated and pre-tested before final interview[25,26,28,29].

2.4. Statistical analyses

The data from the questionnaire were generated into the Statistical Package for the Social Sciences (SPSS Inc., version 17, Chicago, USA) for all statistic analyses. We presented categorical data, like religion, education, occupation, as number and percentages. Continuous data were presented as mean and standard deviation (SD) for normally distributed data and median (interquartile range, IQR) for non-normal data. Odds ratios (*OR*s) and the 95% confidence intervals (*CI*s) were estimated through a logistic regression model to reveal association between different factors like sources of information and levels KAPs. P value <0.05 was considered significant.

2.5. Ethical clearance

This study was approved by the National Ethics Committee for Health Research of the Ministry of Health of Cambodia. Before obtaining oral consent, respondents were explained about the purpose, benefit, and possible harm of the study. Anonymity and confidentiality of their information was maintained. Moreover, all the respondents were given freedom not to participate or to withdraw them from the study at any time.

3. Results

Table 1 shows that among 246 eligible respondents, the median age (IQR) was 28.0 (24.0-34.0) years. Most of them (80.5%) were aged 18-35 years and 182 (74.0%) were Cambodian Buddhist. About 10.2% (25) were illiterate, 140 (56.9%) were educated at primary level and 71 (28.9%) were educated at secondary level. One hundred and forty-nine (60.6%) of them were living with family income less than 60 US dollars per month and the median of their monthly family income was $50.0 (IQR=30.0-75.0). According to occupation, 75.2% of them were housewives, 22.8% were self employed, *i.e.*, they have own businesses at home; and only 2.0% were employed.

Table 2 indicates knowledge of the study population about HPAI relating to modes of transmission, symptoms, treatment and prevention. Only 28.0% respondents could correctly answer about the indirect mode of transmission of HPAI, and more than half of them knew that HPAI transmission by direct contact with sick or dead poultry is possible. Only 2.4% of the respondents had correct knowledge about human-to-human transmission of HPAI. Less than half (41.5%) of the respondents responded that HPAI can be transmitted from mosquito bite, 161 (65.4%) answered correctly that AI transmits from poultry to animals, such as cats, dogs, tigers, lions *etc.*

Respondents were asked about nine symptoms of HPAI in human to assess their knowledge. Only four symptoms of HPAI were commonly known by Cambodian people, such as fever (64.6%), cough (34.6%), breathlessness (23.2%) and muscle ache (23.6%) because these symptoms were mentioned in the IEC materials and were regularly broadcasted on television and radio. Others are described in the leaflets and booklets only. Most of them (n=234, 95.1%) told correctly that HPAI causes death within 48 hours from the onset of symptoms, 156 (63.4%) had the wrong impression that vaccine against HPAI is available in Cambodia and 141 (57.3%) had the right knowledge about availability of drugs for treatment HPAI.

Majority of the respondents (n=162, 65.9%) were aware that avoiding contact with sick or dead bird can prevent HPAI, and 166 (67.5%) felt hand washing, 229 (93.1%) said that wearing mask can prevent themselves from HPAI and only (15.9%) aware that avoiding cock fighting can prevent from HPAI.

Figure 1 shows multiple sources of information about HPAI. Radio was the first source that could provide knowledge on HPAI for the most people (78.9%), followed by television (49.2%).

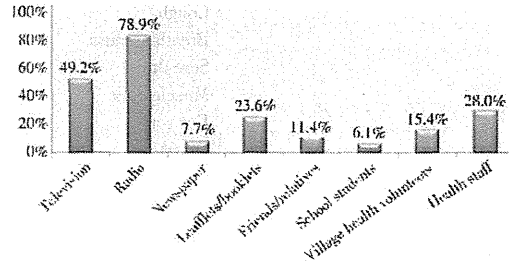

Figure 1. Different sources of information about HPAI.

While questioning about their attitudes on HPAI, 214 (87.0%) opined to meet public health staffs when they get sick, only 10 (4.1%) prefer to use public health services, and 91.5% favor to use private health services. When we asked them about their willingness to visit HPAI patients in the hospital, 49 (19.9%) answered "yes" and 240 (97.6%) were

willing to see a medical doctor if they are suspected with HPAI infection (Table 3).

Table 4 demonstrates practices of the respondents to prevent HPAI. It shows that 134 (54.5%) clean poultry cages every day, 144 (58.5%) collect manure from the cage every day, 95 (38.6%) keep new birds away from the old one more than two weeks, 220 (89.4%) sold sick birds to other people, 215 (87.4%) always cook dead birds for food, 184 (74.8%) of them always throw dead birds into the water or forest, 115 (46.7%) scatter manure in the field, 219 (89.0%) always used

Table 1
Socio-demographic characteristics of the study population (n=246).

	Characteristics	n	%
Age group (years)	18–35	198	80.5
	36–40	23	9.3
	41–45	13	5.3
	46–50	7	2.8
	51–55	5	2.0
Religion	Buddhist	182	74.0
	Muslim	64	26.0
Education	Illiterate	25	10.2
	Primary	140	56.9
	Secondary	71	28.9
	High school	8	3.3
	University	2	0.8
Occupation	Housewife or unemployed	185	75.2
	Self employed/home business	56	22.8
	Employed	5	2.0
Monthly family income (US$)	<60	149	60.6
	⩾60	97	39.4

Table 2
Knowledge of the study population about HPAI.

Factors		Correct answers	
		n	%
Mode of transmission	HPAI can be transmitted through:		
	direct contact with sick or dead birds	145	58.9
	indirect contact *e.g.*, airborne	69	28.0
	eating raw egg	45	18.3
	animals infected with HPAI	161	65.4
	mosquito bite	102	41.5
	human to human	6	2.4
Symptoms of HPAI	Fever	159	64.6
	Cough	85	34.6
	Breathlessness	57	23.2
	Sore throat	36	14.6
	Muscle ache	58	23.6
	Eye sore	10	4.1
	Diarrhea	15	6.1
	Vomiting	10	4.1
	Stomach ache	8	3.3
Treatment and prevention of HPAI	Drugs available for curing HPAI	141	57.3
	Separate wards for AI patients is available in hospitals province	161	65.4
	HPAI can be treated by vaccine	221	89.8
	HPAI vaccine available in Cambodia	90	36.6
	HPAI may lead to death	234	95.1
HPAI can be prevented by:	avoiding contact with sick or dead birds	162	65.9
	washing hands after handling sick or dead birds	166	67.5
	avoiding cock fighting	39	15.9
	washing raw meat properly	57	23.2
	staying away from poultry farm	104	42.3
	cooking well	90	36.6
	cleaning equipment after they were used	58	23.6
	wearing mask during exposure	229	93.1

Table 3
Attitudes on HPAI.

Variables	Respondents with correct answers	
	n	%
Meet public health staff when get sick	214	87.0
Meet traditional healer when get sick	221	89.8
Take over-the-counter flu medication	223	90.7
Do nothing, just stay at home naturally during sickness	220	89.4
Prefer to use private services for treatment of HPAI	225	91.5
Prefer to use public services for treatment of HPAI	10	4.1
Do not hesitate to visit patients with HPAI	49	19.9
Prefer to take care of HPAI patients	218	88.6
See medical doctor when suspected with HPAI	240	97.6
See traditional physician when suspected of HPAI	241	98.0
Buy drugs from pharmacy for prevention of HPAI	240	97.6

Table 4
Practices of the respondents on HPAI.

Variables	Correct answers	
	n	%
Keep poultry with animals	176	71.5
Stay with poultry	176	71.5
Clean poultry cage every day	134	54.5
Always wash hand with soap after touching poultry	228	92.7
Clean outdoor and indoor every day	172	69.9
Collect manure of poultry every day	144	58.5
Keep new birds from the market with the old ones	206	83.7
Separate new birds from the old for < two weeks	92	37.4
Separate new birds from the old ones > two weeks	95	38.6
Always keep sick birds in the cage	130	52.8
Sell sick birds to the others	220	89.4
Cook dead birds for food	215	87.4
Slaughter dead birds and sell in the market	230	93.5
Burn/ burry dead birds	176	71.5
Throw dead birds away	184	74.8
Keep manure in the well	122	49.6
Scatter manure in the field	115	46.7
Always wash eggs before cooking	219	89.0
Always cover your nose when removing feathers of poultry	154	62.6
Always wash equipments after they are used	244	99.2

to wash eggs before cooking, 154 (62.6%) always cover their noses during removing feathers of poultry, and 230 (93.5%) always slaughter dead birds and sell in the market.

Although majority of the subjects (n=196, 79.7%) (8.6±4.0) had positive attitude towards HPAI, only half of them had good knowledge (n=114, 46.3%) (8.6±1.5) and good practices (n=145, 58.9%) (14.0±3.1).

Table 5 shows the contributions of different sources of information on the level of KAP of HPAI of the study population. Most of the sources were significant in increasing knowledge of the respondent, like television, radio, leaflets/booklets, school student, village health volunteers *etc*. Few factors did have similar influence on practices, such as television, leaflets/booklets, and public health staff. Unfortunately, we could not find any significant sources of information which may influence on changing their attitudes.

4. Discussion

Recommendations and guideline developed by WHO in order to control and prevent outbreaks of HPAI have been used in Cambodia in response to the endemic threat due to poor knowledge, negative attitudes, and bad practices[30-32]. The main recommended measures used to apply the public health interventions are: 1) intensify collaboration between animal sector and public health sectors; 2) appropriate personal protective equipment (PPE) for medical workers; 3) effective disease surveillance for early detection and reporting of outbreaks; 4) food safety of poultry products; 5) control of movement of birds and products that may contain viruses; 6) risk communication; 7) rapid destruction of infected poultry and poultry at high risk of infection; and 8)

Table 5
Impact of different sources of information on knowledge, attitudes, and practices of HPAI.

Source of Information	Knowledge					Attitude					Practice				
	Good (%)	Poor (%)	*OR*[+]	95% *CI*[±]	*P* value	Pos[#] (%)	Neg[△] (%)	*OR*	95% *CI*	*P* value	Good (%)	Bad (%)	*OR*	95% *CI*	*P* value
Television	55.3	43.9	1.6	1.0–2.7	0.070	82.6	76.8	1.4	0.7–2.6	0.297	62.1	30.7	3.7	2.1–6.4	<0.001
Radio	86.8	72.0	2.5	1.3–4.9	0.007	81.4	73.1	1.6	0.8–3.3	0.216	80.7	76.2	1.3	0.7–2.5	0.354
Newspaper	10.5	5.3	2.1	0.8–5.5	0.135	89.5	78.9	2.1	0.5–9.6	0.323	10.3	4.0	2.8	0.9–8.8	0.075
Leaflets/booklets	30.7	17.4	2.1	1.2–3.9	0.014	77.6	80.3	0.8	0.4–1.7	0.616	29.7	14.9	2.6	1.4–5.1	0.004
Friends/relatives	13.2	9.8	1.4	0.6–3.0	0.437	82.1	79.4	1.2	0.4–3.4	0.703	11.7	10.9	1.2	0.5–2.7	0.672
J-HSS[##]	12.3	0.8	18.4	2.4–142.9	0.009	80.0	79.7	0.9	0.2–3.5	0.903	8.3	3.0	2.8	0.8–10.2	0.127
VHVs*	25.4	6.8	4.5	2.2–10.9	<0.001	86.8	78.4	1.8	0.7–5.0	0.235	15.9	14.9	1.1	0.5–2.2	0.869
PHSs**	39.5	18.2	2.9	1.6–5.2	<0.001	81.2	79.1	1.1	0.5–2.2	0.809	33.8	19.8	2.2	1.2–4.1	0.011

[+]*OR*: Odds ratio, *OR*s were adjusted for age, educational status, and income of the respondents; [±]*CI*: Confidence interval; [#]Positive; [△]Negative; [##]J-HSS: Junior high school and high school students; *VHV: Village health volunteer; **PHS: Public health staff; [##]Reference category is 'Poor' for knowledge, 'Bad' for practices, and 'Negative' for attitudes.

proper use of vaccination[25,33,34].

The results of our research illustrated that the knowledge of the study population was moderate related to modes of transmission, symptoms, treatment and prevention of HPAI which is in agreement with the similar finding of a study conducted in Thailand among the high-risk population[35]. Nearly half of the respondents correctly answered that HPAI does not spread from mosquito to human. Surprisingly, almost of all the respondents mentioned incorrectly that HPAI can be transmitted from human to human. The low level of awareness of Cambodian women contradicts with the recently published studies in Italy and China which reported higher level of awareness on HPAI among their general population[19,24]. Low level of literacy among our women may be the striking factors behind these contradictions.

The study also showed that just over half of women had good practices. Almost similar level of practices were also reported in a study in Thailand among the high-risk people[35]. Lack of good practices on HPAI is one of the risk factors of contracting and spreading of HPAI. For people who always prepare sick or dead birds for consumption and have direct contact with sick or dead birds without PPEs, the proportion of infection from infected birds could be high[7,8, 19, 36]. People engage themselves in this risky practices specially during the national holidays, Chinese new year and special occasions, and they believe that since long time their seniors and neighbors could never get infected with HPAI by doing that[22]. This may also be strongly related to poor economic status and low literacy rate. A finding of a newly published study in China shows similarity with our results[24].

Linked to the factor of cockfighting, only 16% of the study population was aware that HPAI contaminated from cockfighting. Cockfighting is a very popular game in Cambodia which takes place every year during summer. Although we don't have data of cockfighting gamblers in hand, but based on our observation, we noticed that most of the men join in this game, and they could highly get HPAI virus from their fighting cocks. A previous published study demonstrated that transmission of HPAI to human occur through inhalation of infectious droplets and direct contact by handling fighting cocks and playing with poultry, especially playing with asymptomatic infected ducks[37,38].

This survey demonstrated that the main sources for information of HPAI were radio and television. Almost the same result was found in China and Taif, Saudi Arabia[24,39]. However, the level of information that the respondents learnt from the radio was higher than the previous study; but lower from television[29]. People who watched television, the level of good knowledge, good practice, and positive attitude were higher than those who did not watch television. Similar findings from surveys performed in China and Italy shows television was found to be the most effective way to disseminate information on HPAI, but newspaper indicated a controversy to our results[24,25,35]. Unlike the finding among Nigerian people, about 74% of them reported that newspaper was one of the major sources of information on HPAI[40]. Mainly because of low literacy and poor economy, very few women have the scope to read newspaper. People always feel comfortable and trustful while they exchange their views face-to-face with health staff. Thereby, they can clarify their confusions after cross-checking with those staff. In addition, our study shows that leaflets and health staff could spread information better comparing to the others published materials[24,25,41]. This contradiction may be rooted in the difference of literacy and development stage from those countries.

Our finding shows, a quarter of the respondents know about HPAI transmission by indirect way, meaning to say by air borne or conjunctive deposition of large infectious droplets[7,41]. And the spreading of HPAI maybe highly caused by handling infected poultry without using PPEs, preparation of infected poultry for consumption, living with poultry or domestic animals, like cats, dogs, and hygiene of hand washing and using water containing HPAI viruses[42,43].

Although Cambodian women have moderate level of knowledge and practices, they hold a satisfactory level of positive attitudes which was almost similar with the reports

in Indonesia and China[24,33]; however, study done in Italy (2008) shown higher level of knowledge among them[25]. Because of stronger influence of mass media, like television, radio, communication with health staff, Cambodian women enhance their attitude towards positivity in a greater pace than they do so for knowledge and practices. If the KAP of rural Cambodians continues to be limited, a highly pathogenic mutant HPAI could possibly spread between humans in the future.

To make ongoing awareness creation program more efficient, modification is necessary with greater emphasis on most effective means, like television, radio, and through health staff. Satisfactory level of KAPs obtained through such effective strategy could protect Cambodians from a fatal outbreak of HPAI.

The study confronted several limitations which is worthy of mention. First, we did this study in only one district of Cambodia. Second, we addressed only married female respondents who may not be representative of the Cambodian population. Third, our sample size was small which might be a threat for external validity of the result. Despite all these limitations, we believe our findings may provide a valuable source of information for the policy makers and future researchers.

This study reports a moderate level of knowledge and practices, a satisfactory level of attitudes among Cambodian women on HPAI. Television, radio, leaflets/booklets, VHVs etc had contributed in a differential manner on KAP. KAP on AI may be increased if emphasis on the significant contributors like television, radio *etc* can be strengthened, instead of relying on usual IEC materials. Future researches are encouraged on finding appropriate means to sustain and upgrade the existing positive attitudes among the population towards HPAI.

Conflict of interest statement

We declare that we have no competing interest.

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CASE REPORT

Pathological complete response of locally advanced gastric cancer after four courses of neoadjuvant chemotherapy with paclitaxel plus cisplatin: report of a case

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Abstract We report a case of advanced gastric carcinoma treated successfully by four courses of neoadjuvant chemotherapy (NAC) with paclitaxel and cisplatin. The patient was a 43-year-old man with advanced gastric cancer, clinically diagnosed as P0H0M0CY0T3N2, which had invaded the upper body of the stomach and esophagus. He was entered into a clinical trial and received the following NAC regimen: paclitaxel 80 mg/m^2, and cisplatin 25 mg/m^2, on days 1, 8, and 15, followed by a rest on day 22, as one course. The lymph nodes had reduced in size to 59% after two courses and to 40% after four courses, with no sign of severe toxicity. Subsequently, he underwent D2 total gastrectomy with pancreatico-splenectomy. On microscopic examinations, no tumor cells were detected in the ulcer scar of the resected stomach or the regional lymph nodes. Thus, we discuss the potential of long-term NAC, especially for responders to two initial courses.

Keywords Gastric cancer · Neoadjuvant chemotherapy · Pathological CR

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Introduction

Macroscopic complete tumor removal is essential to cure gastric cancer [1] and primary surgical resection is standard for gastric cancer without distant metastasis [2]. However, curative resection is difficult for locally advanced gastric cancer with lymph node metastases forming a bulky mass around the celiac, common hepatic, or splenic arteries. Even if the tumors can be resected macroscopically, the prognosis is generally poor, suggesting that the tumors already have micrometastasis. For such tumors, neoadjuvant chemotherapy (NAC) followed by surgery is a promising approach that can reduce the size of the tumors and eradicate the micrometastases [3, 4].

Recent advances in chemotherapy have improved the overall survival of patients and/or the response rate for metastatic gastric cancer, encouraging clinicians to try giving NAC, followed by a surgical resection, for locally advanced gastric cancer [5]. However, a pathological complete response (CR) after one or two courses of NAC has rarely been reported [6–11]. We report a case of pathological CR after four courses of NAC with paclitaxel and cisplatin, and discuss the possibilities of long-term NAC, especially for responders to two initial courses.

Case report

A 43-year-old man with a 3-month history of epigastric discomfort was referred to the Kanagawa Cancer Center

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Hospital for investigations. On physical examination, a tumor was palpable in the upper abdomen. Endoscopy and upper gastrointestinal tract series showed type 2 advanced gastric carcinoma invading the upper body of the stomach and esophagus (Fig. 1). A biopsy specimen confirmed poorly differentiated adenocarcinoma. An abdominal computed tomography (CT) scan showed that the gastric tumors had invaded the pancreas and metastasized to the regional lymph nodes, including #1, #3, #7, #9, and #11p, forming a bulky mass (Fig. 2a). To assess the extent of tumor spread, we performed laparoscopy and saw no peritoneal dissemination. Peritoneal lavage cytology revealed no tumor cells in the abdominal cavity. We diagnosed advanced disease (cP0, cH0, CY0, cT4, cN2; cStage IV according to the *Japanese classification of gastric carcinoma*, 2nd English edition [12]). The patient was entered into a clinical trial of NAC. Paclitaxel 80 mg/m^2, and cisplatin 25 mg/m^2, were administered on days 1, 8, and 15, followed by a rest on day 22, as one course. The bulky lymph nodes had reduced in size to 59% of the original mass after two courses of chemotherapy (Fig. 2b) and to 40% of the original size after four courses (Fig. 2c). The patient suffered only grade 2 alopecia (according to the WHO toxicity criteria) during the chemotherapy, which was given in the outpatient clinic. Endoscopy and upper gastrointestinal tract series revealed that the type 2 tumor had disappeared and become a gastric ulcer scar (Fig. 3). Endoscopic biopsy showed no cancer cells in the ulcer.

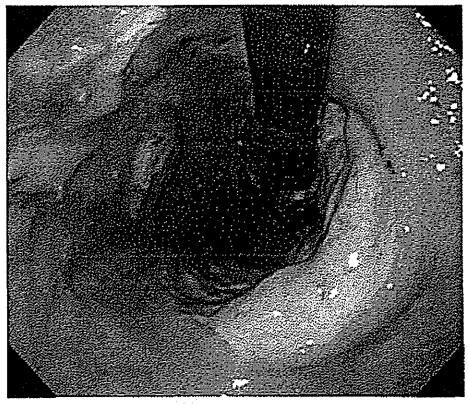

Fig. 1 Endoscopy revealed advanced type 2 gastric carcinoma invading the upper body before treatment

After the completion of chemotherapy, the patient underwent surgery. Peritoneal lavage cytology revealed no cancer cells in the abdominal cavity, but strong adhesion was identified, suggesting that the tumor had penetrated the pancreas. Strong adhesion of the lymph nodes, splenic artery, and pancreas was also observed. The pancreas was resected at the hilum of the splenic artery with curative intent and we then performed D2 total gastrectomy with pancreatico-splenectomy. Macroscopically, ulcer scars were observed in the upper body of the stomach (Fig. 4). Microscopic examination revealed no tumor cells in the ulcer scar of the resected stomach or in any of the lymph

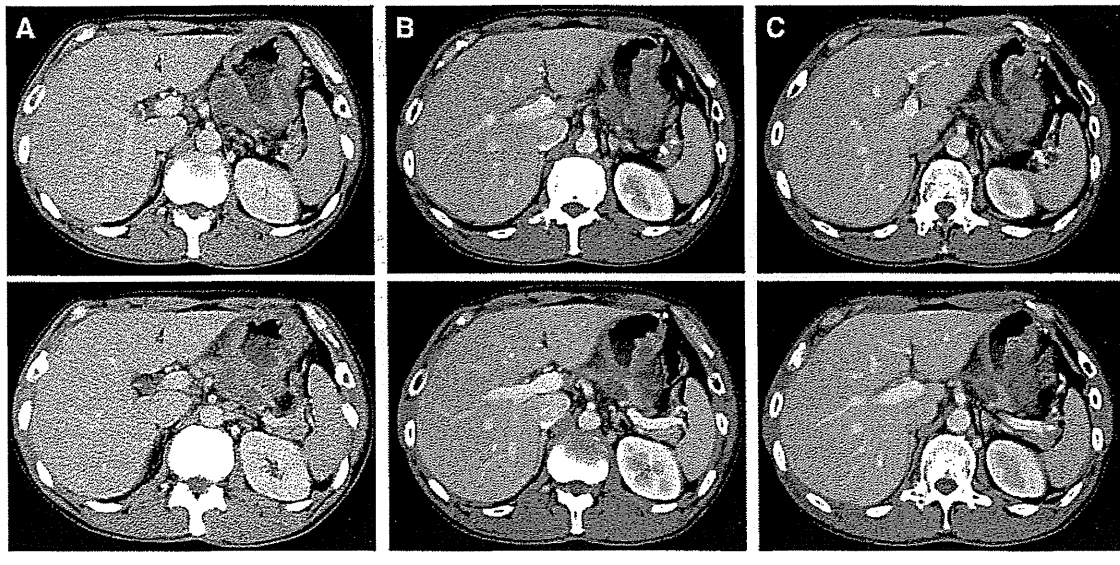

Fig. 2 An abdominal computed tomography (CT) scan showing the regional lymph nodes forming a bulky mass before (a), after two courses (b), and after four courses (c) of chemotherapy. The maximal diameter of the regional lymph node was reduced to 59% of the original size after two courses and to 40% after four courses

nodes harvested from the surgical specimen (Fig. 5), nor were there any tumor cells found on the surgical margins of the resected specimens. The patient recovered uneventfully and is currently receiving adjuvant chemotherapy with S-1, in the outpatient clinic. If he remains well, the S-1 therapy will continue for at least 6 months.

Fig. 3 Endoscopy revealed only a gastric ulcer scar after treatment

The patient who is the subject of this case report was entered into the clinical trial of COMPASS, an on-going multi-center randomized phase II study to compare S1 plus CDDP versus paclitaxel plus cisplatin and two courses versus four courses for locally advanced gastric cancer [13, 14]. This case report was approved by the COMPASS trial committee.

Discussion

In Japan, phase II trials have been conducted to test NAC [6, 7, 15]. The JACCRO GC-01 trial, which assessed the efficacy of only one course of S-1 plus cisplatin in 49 patients with gastric cancer invading the serosa, demonstrated a 39% pathological response rate, but no pathological CR [6]. The JCOG-0001 phase II trial then assessed

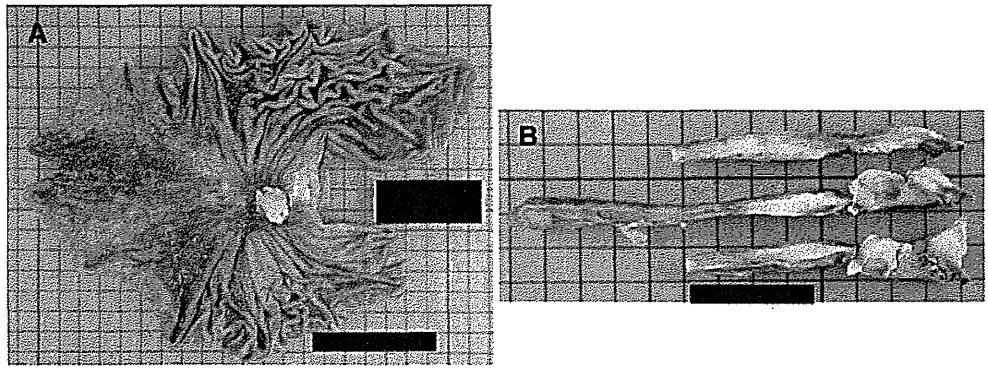

Fig. 4 Photographs of the resected stomach showing ulcer scars on the horizontal (a) and vertical sections (b)

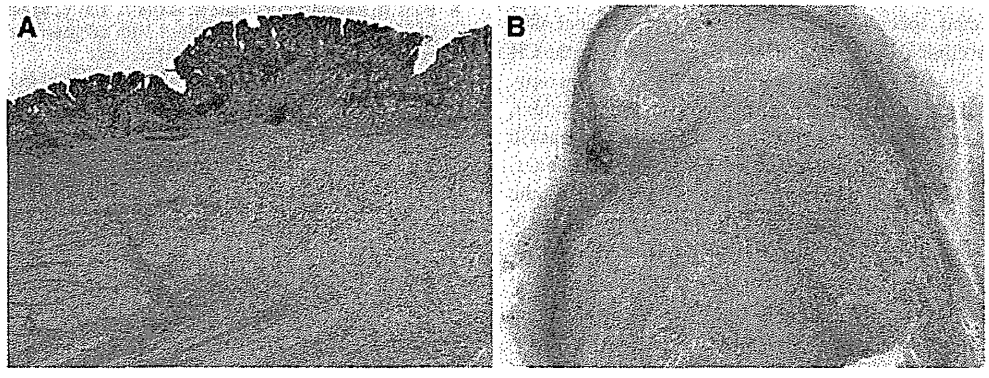

Fig. 5 Photomicrographs showing granulation tissue in which the tumor cells seem to have disappeared in the ulcer scar of the resected stomach (a) and the lymph nodes (b)

the efficacy of two courses of irinotecan plus cisplatin in 55 patients with bulky nodal metastasis, and demonstrated a pathological response rate of 15% but no pathological CR [7]. Several investigators have evaluated the effects of one versus two courses of NAC using S-1 plus cisplatin in retrospective analyses, but no pathological CR was reported [8, 9]. Moreover, there have been only sporadic case reports demonstrating pathological CR after one or two courses of chemotherapy [10, 11]. Therefore, pathological CR is extremely rare following short-term NAC, regardless of the regimen.

Short-term NAC is based on the following evidence-based conclusions: CR is important to improve respectability; CR can be achieved within two courses; resectable tumors should be resected before they progress to become unresectable; and clinical response and resectability are important to improve survival. In the present case, the lymph nodes shrank after two courses of chemotherapy and a CR was achieved. An additional two courses resulted in an even greater reduction in the size of the lymph nodes. If this patient had undergone surgical resection after the initial two courses, the pathological CR might not have been achieved. Thus, the possibility of a pathological CR might be increased by adding two or more courses for tumors that have responded to the two initial courses of chemotherapy. Although long-term chemotherapy may increase the risk of the tumor growing and becoming unresectable, such tumors would be likely to recur soon after short-term chemotherapy and surgical resection. Therefore, long-term chemotherapy may provide another advantage by avoiding unnecessary operations. Moreover, progression-free survival for patients with metastatic disease was reported to be 6.0 months in the S-1 plus cisplatin phase III trial [16] and 5.5 months in the paclitaxel plus cisplatin phase II trial [13]. This suggested a low risk of the rapid tumor growth within four courses.

This case could not be diagnosed as clinical CR because the lymph node metastasis had not completely disappeared on CT, even after four courses of chemotherapy; however, the resected specimen demonstrated a pathological CR. Thus, the clinical diagnosis of CR is difficult because the CR rate may be low for gastric cancer following chemotherapy.

Paclitaxel plus cisplatin, which was given to this patient, is not a general regimen of choice for metastatic gastric cancer or locally advanced disease, but it has been evaluated by only a few phase II studies [17]. Although the response rates vary from 18 to 41%, weekly or biweekly paclitaxel with cisplatin resulted in median overall survival of about 11 months [17]. On the other hand, S-1 plus cisplatin has been the most popular regimen for NAC, since a high response rate was observed in more than 70% of patients with metastatic gastric cancer [18]. Based on the results of several phase III trials, S-1 plus cisplatin has become a standard treatment for metastatic gastric cancer [16, 19]. Therefore, the clinical efficacy of S-1 plus cisplatin might be superior to paclitaxel plus cisplatin, although there have been no clinical trials to compare these two regimens. It remains unclear whether the pathological CR in this case could have been achieved by two courses of S-1 plus cisplatin. It should also be clarified whether the CR rate and prognosis could be improved by four, rather than just two, courses of neoadjuvant chemotherapy. The COMPASS, comparing short- and long-term neoadjuvant chemotherapy, is an ongoing randomized phase II trial, which may answer these questions [13, 14].

Conflict of interest Takafumi Watanabe and his co-authors have no conflict of interest.

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Major article

Antibiotic use in Vietnamese hospitals: A multicenter point-prevalence study

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Key Words:
Prescription
Prevalence
Indication
Vietnam

Background: Inappropriate antibiotic prescribing appears to be common worldwide and is contributing to the selection of resistant organisms. This study examined the prevalence of antibiotic prescription and the appropriateness of indications for these prescriptions in 36 representative general hospitals across Vietnam.

Methods: A point-prevalence study was performed between February and December 2008. All inpatients on the day of the survey were included in the analysis. Standard published guidelines were used to evaluate the appropriateness of indications for antibiotic prescription.

Results: On the day of the study, 5,104 of 7,571 patients (67.4%) were receiving antibiotic therapy. The antibiotic prescription rate was highest in surgery wards (93.2%) and lowest in medical wards (48.2%). Of the 5,104 patients receiving antibiotics, the most commonly prescribed agents were cephalosporins (70.2%), penicillins (21.6%), and aminoglycosides (18.9%). Approximately one-third of the patients (1,573 of 5,104) had an inappropriate indication for prescription. Risk factors independently associated with inappropriate indication for antibiotic prescription were seen in hospitals at the national level, obstetrics and gynecology departments, and surgical wards.

Conclusions: Our data indicate a high rate of antibiotic use in Vietnamese hospitals, and also a high prevalence of inappropriate indications for antibiotic prescriptions. These findings suggest important areas for intervention and implementation of antibiotic stewardship policies in Vietnamese hospitals.

Antibiotics are among the most important advances in medical therapy over the past century.[1,2] They have dramatically changed the prognoses of patients with severe infectious diseases.[3,4] The success of antibiotic treatment has led to the excessive and indiscriminate use of antibiotics in hospitals worldwide.[3,5,6]

Inappropriate use of antibiotics and poor infection prevention and control practices have provided favorable conditions for the development of many strains of resistant microorganisms.[7] The abundant literature is consistent regarding the concept of increasing resistance with increasing antibiotic use.[2,3,7,8] Although antibiotic resistance is rising, there are only a handful of new antibiotics currently in development, all of which are in early stages, with no new class of antibiotic expected to be ready for use in the next 20 years.[6] The emergence and dissemination of resistant organisms has increased the likelihood of antibiotic treatment failure and also increased the rate of adverse drug events.[1,3,4,8,9] Infections with antibiotic-resistant isolates pose a risk of health care–associated spread of infectious pathogens and are associated with increased complications, elevated mortality,[1,3,4] and an increased financial burden to health care facilities, families, and society.[4,6,9] Thus, increasing antibiotic resistance is considered one of today's most challenging problems in medical science, with clinical, economical, and public health implications. Although there is no lack of evidence-based guidelines for appropriate antibiotic use in developing countries, previous studies suggest that up to 50% of antibiotic indications for hospitalized patients do not strictly adhere to these guidelines.[2,3,10] The impact of antibiotic resistance is far more serious in developing countries than in developed countries, with limited resources available to address the increasing frequency and magnitude of the problem.[11,12]

Good antibiotic prescribing practice is the key to reducing the emergence of resistance and ensure the availability of drugs needed

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for the effective management of infectious diseases for current and future generations.[4] Few previous studies have included data on prescribing practices in developing countries, however.[13] Investigation of inappropriate antibiotic use (eg, incorrect quantifying dose, dosage interval, timing, spectrum), as well as whether laboratory and clinical findings support the need for antibiotics, may provide comprehensive data on prescribing practices. In the absence of such detailed investigations, surveys on the appropriateness of indications for antibiotic use (which require less exhaustive resources) can help establish priorities for antibiotic stewardship policies in countries where financial resources and qualified personnel are in short supply. In this regard, point prevalence studies (PPSs) can provide useful insight into antibiotic prescribing patterns.[14] To date, there have been no published reports on the level and appropriateness of indications for antibiotic prescription based on data from representative hospitals in Vietnam. The lack of this information poses a challenge to good antibiotic stewardship in Vietnam. The objectives of this PPS were to determine the prevalence of antibiotic prescription and the appropriateness of indications for prescribed antibiotics among inpatients of Vietnamese hospitals.

METHODS

Setting

Vietnam has 3 levels of hospitals: national (39 general and specialized hospitals), provincial (394 general and specialized hospitals), and district (640 general hospitals). To avoid intrinsic differences among participating hospitals, we included only general hospitals in this study. A list of general hospitals providing medical and surgical services and had an infection control team was obtained from the Vietnamese Ministry of Health and used as a sampling frame. The study protocol was then sent to all selected general hospitals.

We aimed to cover 5% of the total general hospital beds in Vietnam (6,715 of 134,282 beds). We used a stratified random sampling technique to select different general hospitals so that our sample adequately represented national-, provincial-, and district-level hospitals. Accordingly, our target numbers were 973 beds from national-level hospitals (out of 19,460 total beds), 4,630 beds from provincial-level hospitals (out of 92,590), and 1,112 beds from district-level hospitals (out of 22,230). Based on the number of beds and the hospitals' willingness to participate, we randomly selected 2 hospitals from 18 national-level hospitals, 18 hospitals from 177 provincial-level hospitals, and 16 hospitals from 128 district-level hospitals. Finally, we recruited all inpatients from the selected hospitals, resulting in a final sample size of 7,571, slightly higher than the initial target. All inpatients present in the selected hospitals on the day of the study were included in the survey. Lists of patients were obtained between 8:00 AM and 9:00 AM on the morning of the survey day.

Study design

A PPS was performed to identify patients receiving antibiotic treatment. For each facility, the PPS was conducted on a designated day during February through December in 2008.

Evaluation of the appropriateness of indications for antibiotic prescription

To determine the prevalence of antibiotic use among inpatients in participating hospitals, we recorded only antibiotics that were included in the prescription on the day of the survey. Patients were considered as not receiving antibiotic treatment if they did not receive any antibiotic on the day of the survey. Indications for antibiotic prescription were determined to be either appropriate or inappropriate. Guidelines for antibiotic use from the Association for Professionals in Infection Control and Epidemiology were used to evaluate the appropriateness of indications for antibiotic prescription.[15] Medical records, microbiological test results, and drug charts were reviewed to categorize the appropriate indications for antibiotic use as (1) identified pathogen-directed, (2) empirical, or (3) prophylactic. Pathogen-directed therapy described antibiotic indications when the microbial pathogen was determined based on the results of microbiological testing. The antibiotic indication was considered empirical therapy when no information about the causative pathogens was available and the decision to prescribe an antibiotic was presumed to be based on other data or on the physician's experience or judgment. In hospitals with laboratory services, empirical therapy was defined as therapy given when microbiological tests for a causative pathogen were negative and clinical features and supportive data (eg, radiographs, ultrasound scans, endoscopic procedures, pathology reports for biopsy specimens) supported the diagnosis of infection. However, in hospitals without a microbiology laboratory, antibiotics were considered empirical therapy when clinical features and supportive data supported the diagnosis of infection. Antibiotic therapy was defined as prophylactic when it was prescribed to prevent infection in patients who sustained trauma or underwent surgery. Antibiotic prophylaxis in surgical cases was defined as that administered within 30 minutes before surgery. An antibiotic indication was considered inappropriate if it did not meet the criteria for any of the 3 foregoing indications.

Data collection

The aggregated data, including patient characteristics and antibiotic prescriptions, were collected for all inpatients by a trained surveillance team from each hospital comprising an infection control practitioner and a doctor and a nurse from each clinical ward. The following patient characteristics were recorded: age, sex, ward, clinically infected features, and microbiological test results. Data were collected on antibiotic prescriptions for therapeutic or prophylactic purposes, including the number and the class of antibiotics and indications for antibiotic prescription. The major classification of an antibiotic was based on the broad category of microorganisms against which the drug has activity.

Completed data collection forms were checked for accuracy and completeness at the end of the survey day by the principal researcher and the infection control practitioner from the surveyed hospital. This study was reviewed and approved by the Ethics and Health Research Review Committee of the Vietnamese Ministry of Health.

Statistical analyses

All statistical analyses were performed using SPSS version 18 (SPSS Inc, Chicago, IL). The prevalence of antibiotic prescription was defined as the percentage of the number of patients receiving any antibiotic out of the total number of patients studied, and the prevalence of inappropriate indication for antibiotic therapy was defined as the percentage of patients with inappropriate antibiotic indication out of the total number of patients receiving any antibiotic. Differences in proportions were compared using the χ^2 test. Multivariate logistic regression was used to identify relationships between an inappropriate antibiotic indication and the variables studied (ie, age, sex, region, hospital type, and ward). Variables were screened for inclusion in the multivariate model using

bivariate logistic regression models. Candidate variables with $P \leq .25$ were included in the final multivariate model. All reported P values were 2-sided, and a P value <.05 was considered statistically significant.

RESULTS

Patient demographics

A total of 7,571 inpatients were surveyed in 36 hospitals (2 national level, 18 provincial level, and 16 district level), including 3,803 males (50.2%) and 3,768 females (49.8%), with a mean age of 42.3 ± 23.8 years (age range, 2-96 years). There were 4,105 (54.2%) patients on medical wards, 1,910 (25.2%) patients on surgical wards, 694 (9.2%) on pediatric wards, 508 (6.7%) on obstetrics and gynecology wards, and 354 (4.7%) in intensive care units. The majority of the patients surveyed were hospitalized in provincial hospitals (4,676; 61.8%), followed by national hospitals (1,778; 23.5%) and then district hospitals (1,117; 14.8%). Geographically, 70.4% of the patients were from the delta region 17.4% were from the mountain region, and 12.0% were from the midland/highland region.

Prevalence of antibiotic prescription

The overall antibiotic prescription rate was 67.4% (5,104 of 7,571 patients), ranging from 48.2% (1,979/4,105) in medical ward patients to 93.2% (1,780/1,910) in surgery ward patients (Table 1). After adjusting for covariates, antibiotic use varied by ward specialty, with higher rates observed in surgical wards (adjusted odds ratio [aOR], 13.2; 95% confidence interval [CI], 10.9-16.1), obstetrics and gynecology wards (aOR, 5.0; 95% CI, 3.9-6.5), pediatric wards (aOR, 6.8; 95% CI, 5.1-9.0), and intensive care units (aOR, 4.3; 95% CI, 3.3-5.7). Patients in district hospitals (aOR, 2.2; 95% CI, 1.8-2.6) and provincial hospitals (aOR, 1.4; 95% CI, 1.2-1.6) were more likely to receive antibiotics compared with patients in national hospitals. Laboratory services for infection diagnosis were provided at 15 of the 36 participating hospitals (2 national and 13 provincial; 41.7%). Antibiotic prescriptions were less frequent in hospitals with laboratories compared with those without (66.7% [4,156 of 6,233] vs 70.9% [948 of 1,338]); this difference was not significant, however. Antibiotic prescriptions did not vary by age group, sex, or geographic region.

Characteristics of antibiotic prescription

Of the 5,104 patients with an antibiotic prescription, 3,237 (63.4%) received 1 agent, 1,547 (30.3%) received 2 agents, and 320 (6.3%) received 3 or more agents. The most commonly prescribed antibiotic agents were cephalosporin (n = 3,585; 70.2%), penicillins (n = 1,105; 21.6%), aminoglycosides (n = 963; 18.9%), and imidazole (n = 555; 10.9%). Antibiotic indication was deemed inappropriate in 1,573 patients (30.8%). The indication was judged appropriate in 3,531 patients (69.2%), including 2791 (54.7%) for empirical therapy, 546 (10.7%) for prophylaxis, and 194 (3.8%) for pathogen-directed therapy (Table 2).

Risk factors for inappropriate antibiotic indication

After controlling for covariates, several factors were seen to be associated with inappropriate antibiotic indication. Hospital ward was one such factor, with higher rates of inappropriate indication observed in the obstretric and gynecology wards (aOR, 33.0; 95% CI, 23.1-45.6) and surgical wards (aOR, 3.7; 95% CI, 3.2-4.3) compared with medical wards. Hospital type and regions were also independent risk factors for inappropriate indication. When compared with national level, the rate was lower in district-level hospitals (aOR, 0.5; 95% CI, 0.3-0.7). Similarly, the rate was lower in the mountain region (aOR, 0.7; 95% CI, 0.6-0.9) than in the delta and midland/highland regions (Table 3).

Table 1
Prevalence and correlates of antibiotic use in Vietnamese hospitals

Characteristics	Sample (n = 7,571)	Patients with antibiotics, n (%) (n = 5,104)	Adjusted OR (95% CI)
Age group, years			
<30	2,480	2,014 (81.2)	Ref
30-59	2,999	1,874 (62.5)	0.8 (0.7-1.0)
≥60	2,092	1,216 (58.1)	0.7 (0.6-1.0)
Sex			
Female	3,768	2,483 (65.9)	Ref
Male	3,803	2,621 (68.9)	1.2 (1.1-1.3)
Region			
Delta	5,347	3,487 (65.2)	Ref
Midlands and highlands	905	634 (70.1)	0.8 (0.7-1.0)
Moutain areas	1,319	983 (74.5)	1.1 (1.0-1.3)
Hospital type			
National	1,778	905 (50.9)	Ref
Provincial	4,676	3,341 (71.4)	1.4 (1.2-1.6)
District	1,117	858 (76.8)	2.2 (1.8-2.6)
Ward			
Medical	4,105	1,979 (48.2)	Ref
Obstetrics and gynecology	508	428 (84.3)	5.0 (3.9-6.5)
Surgical	1,910	1,780 (93.2)	13.2 (10.9-16.1)
Intensive care unit	354	292 (82.5)	4.3 (3.3-5.7)
Pediatric	694	625 (90.1)	6.8 (5.1-9.0)

DISCUSSION

We found that a large number (67.4%) of hospitalized patients received antibiotics and that 30.8% of those antibiotics were considered inappropriately indicated. The prevalence of antibiotic prescription in this study is similar to that reported in previous studies in developing countries. Those studies focused mainly on the prevalence of antibiotic use, which ranged from 62.8% to 77.8%.[8,16] However, our rate is higher than the prevalence reported in previous studies conducted in European countries (range for individual hospitals, 17.8%-32.0%).[3,12] Furthermore, our investigation revealed an inappropriate indication for antibiotic prescription in 30.8% of the patients receiving antibiotics, much more higher than the rates reported in Malaysia (4.0%),[17] Turkey (14.0%),[8] and Hong Kong (20.0%).[14] The high antibiotic use along with high rate of inappropriate indication for prescription in the present study is of public health concern in Vietnam, given the well-documented association between antibiotic consumption and the emergence and diffusion of multidrug-resistant microorganisms.[3,9] Furthermore, overuse of antibiotics can lead to overuse of injections, with a consequent increase in the use of unsafe needles, which can increase the risk of transmission of blood-borne diseases.[18]

The high antibiotic use and inappropriate indications for antibiotic use in hospitalized patients in Vietnam could be related to several factors. Physicians' ready access to a wide variety of antibiotics without any restrictions is the key factor, with many physicians prescribing antibiotics without microbiological results to guide treatment. Although guidelines/regulations for antibiotic prescribing have been drafted, most have not yet been implemented. Thus, the mindset of physicians has been tuned to the use of antibiotic in all clinical cases, even those with a very low probability of infection. The general public also frequently misuses antibiotics, given the ability to buy antibiotics over the counter without a prescription. Finally, many patients even with fever consider antibiotics to be unique drugs for a quick recovery and

Table 2
Characteristics of antibiotic prescription in participating hospitals

Variable	Patients on antibiotics, n (%) (n = 5,104)
Number of antibiotics	
1	3,237 (63.4)
2	1,547 (30.3)
≥3	320 (6.3)
Antibiotic class and/or agent*	
Cephalosporins	3,585 (70.2)
Penicillins	1,105 (21.6)
Aminoglycosides	963 (18.9)
Imidazole	555 (10.9)
Quinolon	246 (4.8)
Macrolide	128 (2.5)
Sulphonamide	36 (0.7)
Others	305 (6.0)
Indications of antibiotic prescription	
Appropriate indications	3,531 (69.2)
Identified pathogen-directed	194 (3.8)
Empirical	2,791 (54.7)
Prophylactic	546 (10.7)
Inappropriate indications	1,573 (30.8)

*Some patients were prescribed more than one antibiotic.

Table 3
Inappropriate indications for antibiotics and their correlates

Variables	Patients with inappropriate antibiotic treatment, n (%) (n = 1,573)	Patients with appropriate antibiotic treatment, n (%) (n = 3,531)	Adjusted OR (95% CI)
Age group, years			
<30	605 (38.5)	1,409 (39.9)	Ref
30-59	668 (42.5)	1,206 (34.2)	1.0 (0.8-1.1)
≥60	300 (19.0)	916 (25.9)	0.8 (0.7-1.0)
Sex			
Female	889 (56.5)	1,594 (45.1)	Ref
Male	684 (43.5)	1,937 (54.9)	1.6 (0.9-1.8)
*Region			
Delta	1,094 (69.5)	2,393 (67.8)	Ref
Midlands and highlands	168 (10.7)	466 (13.2)	0.8 (0.6-1.0)
Moutain areas	311 (19.8)	672 (19.0)	0.7 (0.6-0.9)
Hospital type			
National	216 (13.7)	642 (18.2)	Ref
Provincial	1,022 (65.0)	2,319 (65.7)	0.8 (0.5-0.9)
District	335 (21.3)	570 (16.1)	0.5 (0.3-0.7)
Ward			
Medical	368 (23.4)	1,611 (45.6)	Ref
Obstetrics and gynecology	369 (23.5)	59 (1.7)	33.0 (23.1-45.6)
Surgical	766 (48.7)	1,014 (28.7)	3.7 (3.2-4.3)
Intensive care unit	49 (3.1)	243 (6.9)	1.0 (0.7-1.4)
Pediatric	21 (1.3)	604 (17.1)	0.2 (0.1-0.3)

exert pressure on physicians to prescribe antibiotics. Thus, considering the situation in Vietnam, limiting antibiotic availability could be an important strategy for decreasing the antibiotic prescription rate and reducing inappropriate antibiotic use. Although mass media awareness is prerequisite to changing the mindset of the general public, implementation of strict regulations and guidelines would be an important first step toward reducing the rate of antibiotic prescribing in hospitals as well as in general practice. Inclusion of special course covering such guidelines and regulations in medical education could be beneficial in this regard.

Our data revealed the lowest rate of antimicrobial use in medical wards. This could be related to preoperative and postoperative antibiotic therapy, which was administered to almost all of our surgical patients, as well as to the lower rate of confirmed infections in patients in medical wards (43.7%) compared with those in pediatric wards (91.5%) and intensive care units (61.0%). It is also interesting to note although the prevalence of antibiotic prescription was lowest in the national-level hospitals, the rate of inappropriate indication for antibiotics was the highest in these hospitals. Likely reasons for the higher rate of inappropriate antibiotic use in national-level hospitals include high-intensity work, high surgery rates, and organizational issues. Universal antibiotic use from the preoperative period to discharge in Vietnam could be a factor in the higher rate of inappropriate antibiotic use in national-level hospitals, which perform significantly more surgeries compared with district and provincial hospitals.[19] Lack of senior staff could be an issue as well. Junior staff (interns and residents) making antibiotic prescribing decisions without the supervision of senior staff may have contributed to the high rate of the inappropriate antibiotic use. Appropriate staffing along with strict supervision over junior staff at national hospitals is needed to counter the trend of inappropriate antibiotic use.

Our findings indicate that inappropriate indication for antibiotics varied by ward specialty, similar to findings reported in previously published studies.[3,8,16] Higher rates of inappropriate indication for antibiotic use were observed in obstetrics and gynecology wards (aOR, 31.8) and surgical wards (aOR, 3.7) compared with medical wards. We hypothesized that this might reflect significant variation across types of wards in terms of adherence to local policies and practices relating to antibiotic stewardship. Furthermore, universal antibiotic use in surgical patients could be the key factor in this higher antibiotic use. Administration of antibiotics without appropriate indication will foster the emergence of resistance in endemic bacteria, putting all patients at risk.[19] Our findings suggest that developing practical antibiotic treatment guidelines combined with continuing intensive education and supervision for surgeons and obstetricians and gynecologists may be effective approaches to addressing the problem of inappropriate antibiotic use in Vietnamese hospitals.

In the present study, broad-spectrum antibiotics, such as cephalosporins, were most commonly prescribed agents, accounting for 70.3% of prescriptions. Physicians' fear of inadequate antibiotic coverage might be a major reason behind this high broad-spectrum antibiotic use,[3] although this was not addressed in the present study. Further research into the knowledge and attitudes of physicians in improving appropriate antibiotic prescription is needed to promote improved antibiotic stewardship policies and practices in Vietnam.

In the present study, 36.6% of the patients receiving antibiotics were prescribed combination therapy, and empirical therapy was the most common indication, similar to previously reported results.[8,16,18] Combination therapy may be related to empirical use without guidance from microbiological test results to define the narrowest possible spectrum of activity.[6,8] The high rate of empirical therapy in Vietnamese hospitals may be related to the limited health care resources of participating hospitals. In many of the hospitals, laboratory services were not available or cultures were obtained only after empirical antibiotic therapy failed. The worldwide epidemics of mutidrug-resistant microorganisms have diminished the probability that standard empirical regimens will cover 100% of the causative pathogens, and poses a challenge for successful empirical therapy.[5,6] Our findings suggest that Vietnamese health care authorities should focus on these important issues and allocate appropriate resources to strengthen the microbiological support for clinicians, given that no new antibiotics are on the horizon to help address this dilemma.

This study has several limitations. First, it did not address the inadequate dose, dosage interval, timing, and spectrum of antibiotic use, or the resistance of the microorganism responsible for

infection at which the antibiotic was directed. Second, the rate of identified pathogen-directed antibiotic prescription is likely underestimated, and thus the true rate of appropriate indication for empirical therapy is overestimated because of a failure to identify infections due to limited health care resources, including laboratory services in some of the participating hospitals. Despite these limitations, we believe that our findings provide an important contribution to understanding the patterns of antibiotic use based on representative general hospitals in Vietnam.

In conclusion, this study indicates that antibiotics are commonly prescribed, broad-spectrum agents are frequently used, and one-third of hospitalized patients in Vietnam receive an antibiotic prescription for an inappropriate indication. In addition, the independent risk factors for inappropriate antibiotic indication that we identified suggest areas for future antibiotic stewardship, such as appropriate staffing at national level, intensive education for surgeons and obstetricians and gynecologists, and additional support for clinical microbiology laboratories. Finally, our findings underscore the need to develop evidence-based guidelines for antibiotic therapy in Vietnamese hospitals.

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Combination Chemotherapy with S-1 and Docetaxel in Advanced Gastric Cancer patient with Peritoneal Dissemination and Malignant Ascites

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Abstract

Background; Combined chemotherapy with S-1 and docetaxel was implemented in patient with advanced or recurrent gastric cancer associated with peritoneal dissemination and malignant ascites.
Methods; S-1 was administered orally at 80 mg/m^2 for 14 consecutive days and docetaxel was administered at 40 mg/m^2 on day 1, followed by a 1-week rest, as one course, and the treatment was repeated until progression or severe toxicity.
Results; Three out of the five patients showed response to the treatment. The three patients with response had diffuse-type tumor according to the Lauren's classification. The median number of treatment courses was 4. The median survival time was 315 days, the median time to treatment failure was 225 days, and the 1-year survival rate was 20%.
Conclusions; These results suggest that combined therapy with S-1 and docetaxel is a promising treatment for advanced or recurrent gastric cancer with malignant ascites and peritoneal dissemination.

Key Words: S-1, docetaxel, advanced gastric cancer, peritoneal dissemination

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Introduction

Peritoneal dissemination is a common pattern of metastasis in patients with advanced or recurrent gastric cancer. Patients with malignant ascites are at a particularly high risk for rapid exacerbation of general condition, leading to poor outcomes.

The JCOG 0106 study was a randomized phase III trial designed to establish whether sequential therapy with methotrexate and 5-fluorouracil (FU) was superior to a continuous intravenous infusion of 5-FU alone as first-line chemotherapy in patients who had advanced or recurrent gastric cancer with peritoneal dissemination[1)]. The median survival time was 10.6 months in the methotrexate plus 5-fluorouracil group, as compared with 9.4 months in the infusional 5-FU group (p = 0.31). Combination of Methotrexate and 5-FU could not have shown superior effect compared to 5-FU therapy. Standard treatment for advanced or recurrent gastric cancer with peritoneal dissemination was therefore, has not been determined to date.

Recent clinical studies in patients with advanced or recurrent gastric cancer have included the JCOG9912[2)] and the SPIRITS trials[3)]. On the basis of these studies, S-1 and cisplatin was established to be the standard therapy for advanced gastric cancer in Japan. Quite a few studies have reported that taxane derivatives are effective for the management of gastric cancer with peritoneal dissemination[4-7)]. A good response to taxanes is primarily attributed to two factors. First, taxanes are particularly effective against undifferentiated type carcinomas, which are often accompanied by peritoneal dissemination[8-9)]. Second, the penetration of taxanes into the peritoneum is high[10)]. However, subgroup analysis to reconfirm the hypothesis for patients with peritoneal dissemination and ascites was not performed in either the JCOG 9912 or SPIRITS trial. In this study, the efficacy and safety of combined chemotherapy with S-1, an oral FU, and docetaxel, a taxane, in patients who had advanced or recurrent gastric cancer with peritoneal dissemination and ascites, those usually lead an extremely poor prognosis.

Methods

The subjects were 5 patients with advanced or re-

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current gastric cancer who received first-line chemotherapy with S-1 plus docetaxel in the Department of Gastroenterology, Fujita Health University from April 2006 through August 2009. All patients had peritoneal dissemination as well as malignant ascites and received 2 or more courses of S-1 plus docetaxel treatment as first-line chemotherapy. S-1 (80 mg/m^2) was given orally on days 1 to 14 of a 21-day cycle and was then withheld from days 15 to 21. Docetaxel (40 mg/m^2) was given as an intravenous infusion on day 1 (Fig. 1). Treatment was repeated at 3-week intervals and continued until the detection of progressive disease or the onset of unacceptable adverse events.

Tumor responses were evaluated on the basis of the results of upper gastrointestinal series and computed tomography. The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) was used to assess antitumor response. The survival time was calculated as the interval from the date of starting treatment to the date of death. The survival rate was calculated by the Kaplan-Meier method. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Results

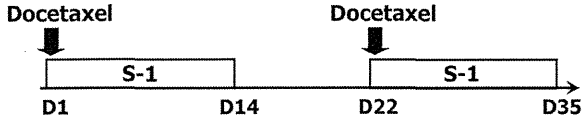
We studied 3 men and 2 women with a mean age of 61 years (range, 58 to 77). The performance status was 0 in 1 patient and 1 in 4 patients. The histopathological diagnosis was signet-ring cell carcinoma in 2, poorly differentiated adenocarcinoma in 1, papillary adenocarcinoma in 1, and tubular adenocarcinoma in 1 patient (Table 1).

As for tumor response, 3 patients had a partial response, 1 had stable disease, and 1 had progressive disease. The overall response rate was 60%. All patients who responded to treatment had diffuse-type, i.e. signet ring cell carcinoma and poorly differentiated gastric cancer (Table 2). The median number of treatment courses was 4 (range, 2 to 7), the median time to treatment failure was 235 days (range, 80 to 346), and the median survival time was 315 days (range, 109 to 558) (Fig. 2). Four patients were subsequently given second-line treatment: 2 received S-1, 1 received S-1 plus cisplatin, and 1 received weekly paclitaxel. The 1-year survival rate was 20% (Table 3). Table 4 shows adverse events according to grade. Grade 3 or 4 adverse events were leukopenia in 2, neutropenia in 1, diarrhea in 1, and nausea in 1 patient.

Discussion

In Japan, the JCOG9912 trial established S-1 to be a key drug for the standard, first-line chemotherapy for advanced or recurrent gastric cancer[1]. Combining S-1 with various types of anticancer agents that have different mechanisms of action has been shown to produce high response rates. S-1 combined with drugs such as cisplatin, irinotecan, or taxanes have been evaluated in phase III studies[2, 8, 9, 11]. The SPIRITS trial already demonstrated that cisplatin enhances the effectiveness of S-1[2]. In contrast, the GC0301/TOP-002 study failed to show that S-1 plus irinotecan was more effective than S-1 alone[11]. Patient enrollment has just been completed in a phase III study examining whether docetaxel enhances the effectiveness of S-1 (START). The results of analysis are awaited.

First-line chemotherapy for advanced or recurrent gastric cancer associated with peritoneal dissemination and malignant ascites remains to be clarified by more robust evidence. Treatment strategies must therefore be based on the results of the phase III trials mentioned above and other studies. Overall, 49% of the patients in the JCOG 9912 trial and 29% of those in the SPIRITS trial had peritoneal dissemination. The results of these phase III studies may provide important clues to the development



Docetaxel: 40mg/m^2 drip infusion within 60min on Day 1
S-1: 80mg/m^2/day orally twice daily, from Day1-Day14
(Drug-free interval, Day15-Day21)
* The administration cycle was repeated every 3 weeks.

Fig. 1. Treatment schedule

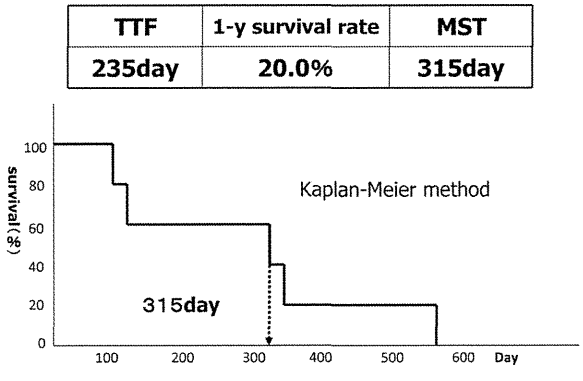


Fig. 2. Overall survival of patients treated with S-1 and docetaxel.
Abbreviations: TTF, time to failure; MST, Median survival time schedule

Table 1. Patient characteristics

Patient's No.	age	Gender	PS	histology
1	74	F	1	pap
2	58	M	1	por
3	59	M	0	sig
4	61	M	1	tub
5	77	F	1	sig

Abbreviations: pap, Papillary adenocarcinoma; por, Poorly differentiated type; sig, Signet-ring cell carcinoma; tub, Tubular adenocarcinoma.

Table 2. Response Rate and histological subtypes

	CR	PR	SD	PD	RR
n=5	0	3	1	1	60%
intestinal	0	0	1	1	0
diffuse	0	3	0	0	60%

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.

Table 3. Therapeutic Efficacy

Patient's No.	Response	TTF (day)	Treatment cycle	2nd line regimen	Survival time (day)
1	PD	88	2	—	109
2	PR	235	3	S-1	315
3	PR	295	7	S-1+CDDP	331
4	SD	80	4	Weekly PTX	125
5	PR	346	7	S-1	558

Table 4. Adverse events

	Grade1	Grade2	Grade3	Grade4	≧G3
leukopenia	1		2		2
neutoropenia	1	1		1	1
anemia		2			
thrombocyto-penia	1				
diarrhea			1		1
nausea			1		1

of new treatment strategies. However, the results of these studies must be interpreted cautiously because the eligibility criteria excluded patients with high-grade peritoneal dissemination.

S-1 has been reported to be effective for diffuse-type gastric cancer, frequently associated with peritoneal dissemination and malignant ascites[12]. Many studies have reported that taxane derivatives are effective against peritoneal dissemination and malignant ascites[8, 9] and that high concentrations of taxanes are transferred to the peritoneum[10]. In particular, docetaxel acts cytotoxically by promoting tubulin polymerization and inhibiting its depolymerization. Docetaxel has been experimentally shown to act synergistically with S-1[13, 14]. In fact, the V325 study demonstrated that docetaxel enhances the effectiveness of standard therapy[15]. A phase II study of docetaxel combined with S-1 obtained an overall response rate of 60.0% in patients who had advanced or recurrent gastric cancer with disseminated peritoneal metastases[16]. Many patients with peritoneal dissemination and malignant ascites have disseminated metastases to the kidney and ureter, frequently precluding the use of cisplatin because of concern about potential adverse effects on renal function. We consider S-1 plus docetaxel to be the treatment of choice in such patients. Our experience suggests that that combined chemotherapy with S-1 and docetaxel has a low incidence of adverse events and can be administered safely.

In our study, patients who responded to the treatment with S-1 and docetaxel showed improved prognosis. The median survival time was 315 days (10.5 months) and, that could be considered as one of the best results for that stage of the disease. All patients with responses had diffuse-type gastric cancer. Our results suggest that S-1 combined with docetaxel is effective and safe in patients with diffuse-type gastric cancer. We consider combined chemotherapy with S-1 and docetaxel to be a safe and promising treatment with a low incidence of adverse events in patients who have severe advanced or recurrent gastric cancer with malignant ascites and peritoneal dissemination, S-1 plus docetaxel may contribute to improve survival even in this subgroup of patients.

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