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Evaluation of Knowledge, Practices, and Possible Barriers among Healthcare Providers regarding Medical Waste Management in Dhaka, Bangladesh

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Background: Improper handling of medical wastes, which is common in Bangladesh, could adversely affect the hospital environment and community at large, and poses a serious threat to public health. We aimed to assess the knowledge and practices regarding medical waste management (MWM) among healthcare providers (HCPs) and to identify possible barriers related to it.

Material/Methods: A cross-sectional study was carried out during June to September, 2012 including 1 tertiary, 3 secondary, and 3 primary level hospitals in Dhaka division, Bangladesh through 2-stage cluster sampling. Data were collected from 625 HCPs, including 245 medical doctors, 220 nurses, 44 technologists, and 116 cleaning staff who were directly involved in MWM using a self-administered (researcher-administered for cleaning staff), semi-structured questionnaire.

Results: Nearly one-third of medical doctors and nurses and two-thirds of technologists and cleaning staff had inadequate knowledge, and about half of medical doctors (44.0%) and cleaning staff (56.0%) had poor practices. HCPs without prior training on MWM were more likely to have poor practices compared to those who had training. Lack of personal protective equipment, equipment for final disposal, MWM-related staff, proper policy/guideline, and lack of incinerator were identified as the top 5 barriers.

Conclusions: Strengthening and expansion of ongoing educational programs/training is necessary to improve knowledge and practices regarding MWM. The government should take necessary steps and provide financial support to eliminate the possible barriers related to proper MWM.

MeSH Keywords: **Awareness • Bangladesh • Communication Barriers • Knowledge • Medical Waste • Practice Guideline**

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Background

The wastes generated during the process of diagnosis, treatment, operation, or immunization or in research activities, are termed as medical wastes [1,2]. It is an ongoing problem for many countries and poses a serious public health problem. Due to modernization of medical services and increased number of patients, healthcare institutions generate large amounts of medical wastes. Approximately 75–95% of bio-medical wastes are non-hazardous and the remaining 10–25% are hazardous to humans or animals and detrimental to the environment [3–5]. It is very important to realize that if both of these types are mixed together, then all waste becomes harmful [6]. Reports in the literature shows 80% of all medical wastes are mixed with general wastes [7].The World Health Organization (WHO) estimated that, during 2000, injections with contaminated syringes caused 21 million hepatitis B virus infections, 2 million hepatitis C virus infections, and 260 000 cases of human immunodeficiency virus (HIV) infections [8]. Cases with staphylococcal bacteriemia and endocarditis were reported among cleaning staff after needle injury [9].

Healthcare providers (HCPs) are at risk of occupational dangers as they perform their jobs in hospitals. Serious diseases may develop in HCPs as well as patients and the general public. The highest rates of occupational injury among all workers who may be exposed to healthcare wastes were reported by cleaning personnel and waste handlers; the annual rate in the United States was 180 per 1000 [10].

Based on types of wastes and hospital category, medical waste management (MWM) scenarios at hospitals in Bangladesh are not satisfactory. There are approximately 1300 government hospitals with 43 000 beds, including public specialized hospitals, medical college hospitals (tertiary level), district hospitals (secondary level), and upazila (primary level) health complexes in Bangladesh. Many private hospitals and clinics also provide healthcare. The waste generation rate for infectious waste and sharps waste from government hospitals were 0.11and 0.03 kg/bed/day, respectively [11]. Most health facilities do not have adequate and effective systemic approaches to medical waste disposal. The medical wastes are simply mixed with the municipal wastes in the collecting bins at the road side and some percentage are buried without any precautions or are burned in the open [12]. The pollution of the environment with toxic substances is a serious public health problem in Bangladesh. Public awareness of healthcare wastes has grown recent years, especially with the emergence of acquired immunodeficiency syndrome (AIDS). In the past 10 years, due to increased number and size of healthcare facilities, medical services and use of medical disposable products, the generation of healthcare wastes has increased rapidly. The Ministry of Health and Family Welfare, Bangladesh, started to address the MWM as a priority program. HCPs has become part of the extensive MWM-related training program and logistics, including different colored bins, were supplied among the healthcare institutions; however, the situation is not yet satisfactory [12,13].

Very few studies had reported on different isolated components of MWM in Bangladesh. One study [14] reported on the health effect of medical practices towards medical wastes. Another study [12] identified the types and amount of medical waste generation. There has been no published study among HCPs regarding awareness of knowledge and practices, and possible barriers to proper MWM in Bangladesh. The WHO recommended raising awareness of medical waste risks and promoting safe and sound practices to improve the situation [15].Therefore, it was necessary to conduct this study with the objective of assessing relevant knowledge and practices, and to identify possible barriers to proper MWM among HCPs. The association of knowledge and practices with background characteristics was also evaluated.

Material and Methods

This cross-sectional study was conducted from June to September, 2012 among different level hospitals in Dhaka division, Bangladesh. A 2-stage cluster sampling method was used to select different levels of hospitals. One tertiary level hospital was selected purposively from Dhaka city. In the first stage, 3 out of 17 district (secondary level) hospitals were selected using a simple random sampling (SRS) method. In the second stage, we also selected 3 upazila (primary level) hospitals, 1 from each of the above-mentioned districts, by applying the SRS.

Subjects

Medical officers, including post-graduate medical students, nurses, technologists, and cleaning staff related to MWM, were recruited from enrolled hospitals. We included those who worked directly with MWM (e.g., involved in clinical activities including pathological/ radiological and cleaning), the permanent employees (except cleaning staff working in tertiary level hospitals, as most of them are on contact basis and post-graduate medical students) of the hospitals and working at least 1 year. A total of 1250 were eligible from all hospitals after excluding those who were not willing to participate. We predetermined that at least 50% of eligible HCPs needed to be included in our study. We selected HCPs at different level hospitals according to their profession and reached our target sample by applying SRS. Finally, we recruited 625 HCPs, including 245 medical doctors, 220 nurses, 44 technologists, and 116 cleaning staff.

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Instrument and data collection

A self-administered, semi-structured questionnaire was adapted from other studies [16–18] with little modification to fit the situation in Bangladesh. A researcher-administered questionnaire was used among cleaning staff since most have little education. The questionnaire had 4 parts. The first part consisted of background information. The second and third parts covered the knowledge questions (12 items) and practice questions (8 items) regarding MWM, respectively. The fourth part consisted of possible barriers. The questionnaire was translated into the local language (Bangla) and back-translated to English to reduce the risk of misinterpretation. The questionnaire was pretested with 25 subjects at different hospitals, and necessary amendments were made accordingly. The content validity of the questionnaire was assessed by a panel of experts in the field. Reliability was assessed by using Cronbach's alpha. The values were 0.64 for practice items and 0.86 for barrier items.

Data were collected by 6 staff, 2 in each level of hospital. They were trained extensively in how to collect data and were pretested in the field before actual data collection. Face-to-face interview was conducted for the cleaning staff only, considering their level of education; otherwise, the self-administered approach was used. To maintain harmony and consistency, they were mutually engaged so that everyone could collect data from all level hospitals. The principal investigator led the supervision to ensure high accuracy in data collection.

Statistical analysis

The Statistical Package for Social Science (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses. Chi-square test was used to compare the categorical data, including age and duration of working among groups. Knowledge scores and practice scores were calculated by giving "1" for a correct answer and "0" for an incorrect answer to each item. Total knowledge score and total practice score were computed for each participant. Mean (±standard deviation, SD) scores were computed for knowledge and practices for all groups of HCPs. Inadequate knowledge and poor practice were defined as correctly answering less than 60% of knowledge items (scoring less than 8 out of 12 points) and practice items (scoring less than 5 out of 8 points), respectively [18,19]. A bivariate logistic regression model was used to estimate odds ratios (ORs) of having inadequate knowledge and poor practices regarding MWM. All tests were 2-sided, and statistical significance was considered at $P<0.05$.

Ethics clearance

The study was approved by the ethical review committee of the National Institute of Preventive and Social Medicine, Mohakhali, Dhaka. Before data collection, informed written consent was obtained from the respondents. Objectives, procedure, risks, and benefits of participating in the study were explained. They were assured that participation was voluntary and they were free to withdraw at any time without any negative consequences. Moreover, confidentiality of collected data was maintained with highest priority. Privacy of the participants was also maintained during data collection.

Results

Background information

Most of the respondents were female (61.4%). Males were more common among doctors and technologists, whereas females were more common among nurses and cleaning staff. Mean (±SD) age of the respondents was 32.3 (±8.0) years. Nurses were younger than the other HCPs ($P<0.001$). Approximately one-third of the respondents were college graduates or above. Almost half of the medical doctors and technologists were working in medicine departments (48.3%) and laboratory/blood banks (49.2%), respectively. Medical doctors had more working experience (>18 years) than the others, while cleaning staff had the lowest working experience ($P<0.001$). Background characteristics are presented in Table 1.

Knowledge regarding MWM

The mean knowledge score (±SD) of the respondents was 7.70 (±1.94). Medical doctors had the highest mean knowledge score (8.22; SD ±1.70), whereas cleaning staff had the lowest (6.14; SD ±1.83) ($P<0.001$). Figure 1 demonstrates that at least one-third of medical doctors and nurses, and nearly two-thirds of technologists and cleaning staff had inadequate knowledge. The lowest percentage of correct answer for both nurses (43.2%) and cleaning staff (9.5%) was with the item of treatment before disposal, whereas the lowest percentage of correct answers for medical doctors (36.7%) was with disposal of human body parts, and the lowest percentage of correct answer for technologists (38.6%) was with hazardous medical wastes (Table 2).

Practices regarding MWM

Mean (±SD) practice score of HCPs was 4.71 (±1.64). Nurses had the highest practice mean score of 5.29 (±1.31) and cleaning staff had the lowest (4.18; SD ±1.54). Figure 1 shows that nearly half of the medical doctors (44.0%) and more than half of the cleaning staff (56.0%) had poor practices. The lowest percentage of correct practice in all 4 groups was with the item of bending/crushing/burning the used needles; percentages were 26.1%, 19.5%, 22.7%, and 21.6% for medical doctors, nurses, technologists, and cleaning staff, respectively (Table 3).

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Table 1. Background information of healthcare providers regarding medical waste management.

Variables	Medical Doctors (n=245) N (%)	Nurses (n=220) N (%)	Technologists (n=44) N (%)	Cleaning staff (n=116) N (%)	P-value*
Gender					<0.001
Female (n=384)	97 (39.6)	188 (85.5)	9 (20.5)	90 (77.6)	
Male (n=241)	148 (60.4)	32 (14.5)	35 (79.5)	26 (22.4)	
Age (year)					<0.001
<30	92 (37.6)	111 (50.5)	12 (27.3)	36 (31.0)	
30–40	119 (48.6)	77 (35.0)	25 (56.8)	46 (39.7)	
>40	34 (13.9)	32 (14.5)	7 (15.9)	34 (29.3)	
Duration of working (year)					<0.001
<8	70 (28.6)	57 (25.9)	17 (38.6)	54 (46.6)	
8–18	70 (28.6)	104 (47.3)	17 (38.6)	16 (13.8)	
>18	105 (42.9)	59 (26.8)	10 (22.7)	46 (39.7)	
Training received					<0.001
No	159 (64.9)	50 (22.7)	13 (29.5)	50 (43.1)	
Yes	86 (35.1)	170 (77.3)	31 (70.5)	66 (56.9)	
Hospital level					<0.001
Tertiary	200 (81.6)	161 (73.2)	20 (45.5)	82 (70.7)	
Secondary	21 (8.6)	36 (16.4)	18 (40.9)	26 (22.4)	
Primary	24 (9.8)	23 (10.5)	6 (13.6)	8 (6.9)	

* Chi-squared test.

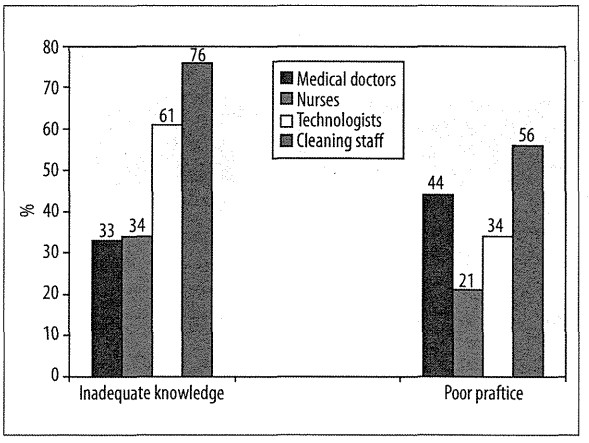

Figure 1. Distributions of inadequate knowledge and poor practices among healthcare providers regarding medical waste management (n=625). Inadequate knowledge and poor practice were defined as correctly answering less than 60% of knowledge items (scoring less than 8 out of 12 points) and practice items (scoring less than 5 out of 8 points), respectively [18,19].

Associations of inadequate knowledge and poor practices with background characteristics

Table 4 shows the ORs of background characteristics for inadequate knowledge and poor practices. Males, older people (30 years and above), technologists, cleaning staff, and district hospitals were more likely to have inadequate knowledge compared to females, younger age, medical doctors, and tertiary hospitals, respectively after being mutually adjusted for gender, age, profession, length of working, training, and type of hospital. Moreover, nurses (adjusted OR, 0.40; P<0.001) were less likely to have poor practices than to medical doctors. However, after mutual adjustment for gender, age, profession, duration of working, training, and type of hospitals, we found that middle-aged people (30–40 years; adjusted OR, 1.66; P<0.008) and those who did not receive training (adjusted OR, 2.43; P<0.001) were more likely to have poor practices.

Possible barriers to MWM

The barriers are demonstrated in Table 5. Insufficient personal protective equipment (PPE) in the hospitals, lack of equipment

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Table 2. Correct answers provided by the healthcare providers on knowledge about medical waste management.

Questions	Medical Doctors (n=245) N (%)	Nurses (n=220) N (%)	Technologists (n=44) N(%)	Cleaning staff (n=116) N(%)	P-value*
Do you know about infectious medical wastes?	233 (95.1)	203 (92.3)	40 (90.9)	93 (80.2)	<0.001
How frequently are wastes removed from source of origin?	195 (79.6)	203 (92.3)	40 (90.9)	93 (80.2)	<0.001
Which one is radioactive medical waste?	213 (86.9)	153 (69.5)	24 (54.5)	76 (65.5)	<0.001
How frequently are wastes removed from central store?	179 (73.1)	151 (68.6)	35 (79.5)	97 (83.6)	0.012
Which one is not transmitted through contaminated syringes?	216 (88.2)	164 (74.5)	30 (68.2)	38 (32.8)	<0.001
Can you define medical wastes?	150 (61.2)	161 (73.2)	28 (63.6)	78 (67.2)	0.053
Do you know about personal protective equipment?	174 (71.0)	137 (62.3)	23 (52.3)	56 (48.3)	<0.001
What is the proper condition to remove the bin?	143 (58.4)	166 (75.5)	18 (40.9)	35 (30.2)	<0.001
Do you know how to treat the infectious waste?	143 (58.4)	118 (53.6)	21 (47.7)	74 (63.8)	0.177
Do you know about hazardous medical wastes?	169 (69.0)	100 (45.5)	17 (38.6)	34 (29.3)	<0.001
Do you know how to dispose of human body parts/IUD**?	90 (36.7)	127 (57.7)	21 (47.7)	27 (23.3)	<0.001
Do you know how to treat waste before final disposal?	107 (43.7)	95 (43.2)	15 (34.1)	11 (9.5)	<0.001

* Chi-squared test; ** IUD – intra-uterine death.

Table 3. Correct answers provided by the healthcare providers about practices on medical waste management.

Items	Medical Doctors (n=245) N (%)	Nurses (n=220) N (%)	Technologists (n=44) N (%)	Cleaning staff (n=116) N (%)	P-value*
Put needle into a special box	186 (75.9)	196 (89.1)	33 (75.0)	90 (77.6)	0.002
Consider as hazardous if accidentally mixed	200 (81.6)	188 (85.5)	19 (43.2)	74 (63.8)	<0.001
Put infectious wastes into a special box	166 (67.8)	195 (88.6)	34 (77.3)	80 (69.0)	<0.001
Sort out medical waste correctly	147 (60.0)	195 (88.6)	39 (88.6)	89 (76.7)	<0.001
Labeling the bin for different types of waste	145 (59.2)	173 (78.6)	27 (61.4)	42 (36.2)	<0.001
Informed higher authority if injured by sharp	100 (40.8)	96 (43.6)	28 (63.6)	52 (44.8)	0.048
Remove as hazardous if not identify correctly	78 (31.8)	76 (34.5)	20 (45.5)	30 (25.9)	0.105
Bending/burning/crushing the used needles	64 (26.1)	43 (19.5)	10 (22.7)	25 (21.6)	0.397

* Chi-squared test.

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Table 4. Associations of inadequate knowledge and poor practices with background characteristics of the respondents.

Variables	Inadequate knowledge		Poor practices	
	Adjusted OR*	P-value	Adjusted OR	P-value**
Gender				
Female	1	Reference	1	Reference
Male	1.24	0.247	1.02	0.906
Age (year)				
<30	1	Reference	1	Reference
30-40	1.50	0.036	1.66	0.008
>40	1.92	0.010	1.62	0.052
Profession				
Medical Doctors	1	Reference	1	Reference
Nurses	1.14	0.564	0.40	<0.001
Technologists	2.96	0.002	0.80	0.539
Cleaning staff	6.60	<0.001	1.62	0.049
Training received				
Yes	1	Reference	1	Reference
No	1.25	0.212	2.43	<0.001
Hospital level				
Tertiary	1	Reference	1	Reference
Secondary	1.92	0.008	0.89	0.659
Primary	0.93	0.805	0.89	0.702

* OR – Odds ratio; adjusted mutually for gender, age, length of working, profession, training received and hospital types; ** P value from Wald statistic. Inadequate knowledge and poor practice were defined as correctly answering less than 60% of knowledge items (scoring less than 8 out of 12 points) and practice items (scoring less than 5 out of 8 points), respectively [18,19].

Table 5. Possible barriers of medical waste management identified by the respondents.

Possible barriers	Medical Doctors (n=245) N (%)	Nurses (n= 220) N (%)	Technologists (n= 44) N (%)	Cleaning Staff (n= 116) N(%)	P-value*
Insufficient PPE** in the hospital	140 (57.1)	153 (69.5)	18 (40.9)	69 (59.5)	<0.001
Lack of instrument for final disposal	128 (52.2)	124 (56.4)	28 (63.6)	58 (50.0)	0.018
Insufficient MWM-related staff	131 (53.5)	121 (55.0)	24 (54.5)	54 (46.6)	<0.001
Lack of guideline/policy	132 (53.9)	112 (50.9)	26 (59.1)	55 (47.4)	0.122
Lack of incinerator	113 (46.1)	116 (52.7)	26 (59.1)	63 (54.3)	0.003
Lack of vaccination program for healthcare providers	79 (32.2)	102 (46.4)	24 (54.5)	61 (52.6)	<0.001
Insufficient recycle bin/container	52 (21.2)	67 (30.5)	9 (20.5)	14 (12.1)	<0.001
Insufficient space in store room	40 (16.3)	41 (18.6)	4 (9.1)	10 (8.6)	<0.001
Lack of cooperation from local authority	21 (8.6)	19 (8.6)	1 (2.3)	17 (14.7)	<0.001
Lack of autoclave	20 (8.2)	23 (10.5)	5 (11.4)	3 (2.6)	0.020

* Chi-squared test; ** PPE – personal protective equipment.

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for final disposal, insufficient MWM-related staff, lack of guideline or policy, and lack of an incinerator were identified as the top 5 barriers by the respondents. However, the rank order of the barriers differed among the groups. Insufficient PPE in the hospital was the top barrier among all groups except for technologists, whereas insufficient MWM-related staff was the major barrier ($P < 0.001$). There were significant differences among different groups of HCPs regarding possible barriers, except for lack of policy/guideline ($P < 0.05$).

Discussion

To our knowledge, this is the first study to assess the knowledge, practices, and possible barriers regarding MWM among HCPs in Bangladesh. Our study found inadequate knowledge and poor practices among HCPs regarding MWM. We also identified several possible barriers about MWM – insufficient PPE, lack of equipment for final disposal, insufficient MWM-related staff, and lack of guideline/policy.

Inadequate knowledge was observed more among technologists and cleaning staff than medical doctors and nurses. which is congruent with past studies [9,20]. This inadequate knowledge could be due to low level of general education and, in particular, the basic understanding regarding MWM. Moreover, it was reported in 1994 that improper waste management was attributed more to the negligence of local HCPs [21]. This study also reported that medical doctors had better knowledge than other professional groups, whereas cleaning staff had disquietingly inadequate knowledge. These findings are in line with previous studies [22–24].This might be due to higher technical knowledge among medical doctors than other professional groups. A better knowledge among medical doctors regarding infectious wastes, radioactive wastes, and diseases transmitted through contaminated syringes was observed. However, this study also revealed lack of knowledge among medical doctors regarding MWM in different areas such as proper disposal of human body parts, treatment before disposal, treatment of infectious wastes, and removal of bin/wastes from inside the hospitals. This inadequate knowledge could be due to lack of training during employment, and lack of proper waste management guidelines, as well as lack of discussion on details of harmful effects in general education.

Poor practice was observed among medical doctors, technologists, and cleaning staff, which is in line with a previous study [18]. Deficient practice among cleaning staff might be due to work load, shortage of cleaning staff relative to patients, lack of necessary equipment, and lack of strict supervision and training. Another important reason is that most of the waste handlers are lower socio-economic status with large family size, and lower level of education and knowledge. Most of the time, cleaning staff handle wastes without using necessary PPE [25]. Since medical wastes are usually mixed with municipal general wastes and are dumped together on vacant land in Bangladesh, the HCPs are sometimes reluctant to properly sort waste. Lack of a proper attitude, due to lack of motivation, could also be an important factor behind these poor practices. Even with adequate knowledge, HCPs may underestimate the importance of safe waste handling. Moreover, the possible reasons for better practices among nurses could be due to the maximum time spent in the clinical ward and closely handling the patients; therefore, risk of acquiring infection was greater than for other staff. However, their role was to protect themselves and at the same time, reduce the exposure risk associated with waste for other HCPs, patients, and attendants [26]. Medical doctors had worse practices than nurses, which could be due to lack of awareness about MWM. There is a tendency among medical doctors to overlook proper waste management in Bangladesh because it is a common perception that dealing the issues of medical wastes is not a doctor's responsibility; therefore, most of the time they neglect this issue.

The top 5 barriers identified by HCPs were insufficient PPE, lack of instruments for final disposal, lack of staff, lack of appropriate guidelines, and lack of incinerators. However, the rank of barriers varied according to profession. Insufficient PPE was identified as the most serious barrier by HCPs except technologists, who identified lack of instruments for final disposal. This could be due to insufficient supply of PPE in the hospital relative to patient turnover, ignorance of this issue, improper hospital management by local administration, and insufficient monitoring and evaluation of the logistics related to MWM by central administration. A study in Bangladesh [25] reported that only 18% of HCPs always use gloves and masks when handling medical wastes; 29% use gloves, masks, and other protective equipment in special cases; and more than half of the providers handle infectious wastes with bare hands. That study also reported there were inadequate instruments for treatment of infectious wastes and sharps in a tertiary hospital and only 11% of hospitals used an incinerator. Moreover, the study findings indicated that no guidelines were strictly followed for proper management of MWM in Bangladesh, which is consistent with the present study.

The selection of all 3 levels of hospitals, recruiting subjects by using SRS procedure, and using pre-tested and validated previously published questionnaire are major strengths of this study. However, measuring responses with a psychometric scale such as the Likert scale and its analysis using ordinal regression model could be the better option to extract more meaningful and useful findings from our study, lack of which is a major limitation of the study. Second, this study was limited to only some hospitals of Dhaka division, which may limit generalizability. Third, we could not include private hospitals and MWM could

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be different in those hospitals. Fourth, practice score might be overestimated in our study because it was assessed by self-report. Finally, due to technical jargon, variations in the interpretation of the questionnaire among different level HCPs might be another limiting factor. However, prior training of the data collection staff could resolve this issue significantly. Despite these limitations, our study findings could be used as baseline information for future researchers and policy makers.

Conclusions

Inadequate knowledge and poor practices were observed among HCPs in Bangladesh. Inadequate knowledge and poor practices were more prevalent among technologists and cleaning staff than medical doctors and nurses. Insufficient PPE, lack of instruments for final disposal, lack of staff, lack of appropriate guidelines, and lack of incinerators were identified as the top 5 possible barriers. Practice-based training regarding MWM is needed among HCPs, especially technologists and cleaning staff, to improve the safe disposal of medical wastes. Moreover, government should take necessary steps to remove the possible barriers of proper MWM.

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Conflict of interest

The authors declare no conflict of interest.

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Efficacy of corticosteroids for cancer-related fatigue: A pilot randomized placebo-controlled trial of advanced cancer patients

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ABSTRACT

Objective: Cancer-related fatigue (CRF) is a common and one of the most important issues in palliative medicine, and it has been demonstrated to have a significant impact on patient quality of life (QoL). The present pilot randomized controlled study evaluated the efficacy and toxicity of methylprednisolone (MP) for CRF in advanced cancer patients.

Method: Our study was planned as a randomized, double-blind, multicenter, placebo-controlled trial. Patients were randomly assigned to an MP group, who received 32 mg/day of MP orally for 7 days, and a placebo group. The primary endpoint was an improvement in visual analog scale (VAS) score for fatigue from baseline to day 7. The secondary endpoints were improvements in appetite loss and QoL as well as evaluating the safety of corticosteroids as palliative therapy.

Results: It was not possible to complete patient registration. In total, 35 patients were randomly assigned to an MP group ($n = 18$) and a placebo group ($n = 17$). The mean changes in VAS score for fatigue were −9.06 in the placebo group and −1.56 in the MP group, and for appetite loss −6.44 in the placebo group and −8.06 in the MP group. In addition, there was no evidence that methylprednisolone improved appetite loss or QoL compared to placebo. The incidence of adverse effects was not greater in the MP group.

Significant of Result: We conclude that our sample size was too small to prove the efficacy of methylprednisolone in improving fatigue. Our results were reported as a pilot study performed to support a subsequent larger trial.

KEYWORDS: Cancer-related fatigue, Corticosteroids, Methylprednisolone, Palliative care

INTRODUCTION

The National Comprehensive Cancer Network defines cancer-related fatigue (CRF) as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional

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to recent activity and which interferes with usual functioning (Levy et al., 2012). CRF is one of the most common and important issues in palliative medicine and has a significant impact on patient quality of life (QoL) (Campos et al., 2011). It can occur due to the side effects of treatment or directly as a result of the disease. The prevalence of fatigue has been reported to range from 10 to 56% in a heterogeneous population of cancer patients (Cella et al., 2001; Andrykowski et al., 2005; Yeh et al., 2011; Fernandes et al., 2006); however, the profile of CRF is unclear, as the frequency of the condition is likely to vary depending on the assessment method and threshold. Since the definition of "fatigue" is quite subjective, it is difficult to establish evidence supporting interventions for CRF from the viewpoint of outcome measurements. Another problem in conducting clinical trials to assess CRF is that clinicians do not wish to add the burden of participating in a clinical trial for patients who are undergoing palliative care. Reports of promising pharmacological treatments for CRF, such as methylphenidate (Bruera et al., 2003; 2013; Johnson et al., 2010; Sarhill et al., 2001), erythropoietin, and darbepoetin (Esquerdo et al., 2011; Revicki et al., 2012), have been published, but these studies included a small sample size from which it was impossible to draw any definitive conclusions. Minton and colleagues (2010) also concluded that the safety concerns and side effects of these drugs prevent them from being recommended in the treatment of CRF. Larger randomized control trials are therefore needed before these drugs can be recommended for use in patients with CRF.

While there is little evidence regarding palliative care in CRF, administration of corticosteroids has empirically been used in patients with CRF, and it is taken for granted that most physicians believe in the effectiveness of steroid treatment. The results of a randomized clinical trial (RCT) evaluating the efficacy of dexamethasone for CRF were recently reported by Yennurajalingam et al. (2013) in which total Functional Assessment of Chronic Illness–Fatigue (FACIT–F) (Debb et al., 2011) scores were significantly improved in the dexamethasone group compared to placebo. These results are substantial and meaningful for the many clinicians who provide palliative care for cancer patients.

We previously conducted a similar RCT from 1999 to 2003 that was strictly designed to verify the effectiveness of methylprednisolone for CRF, the results of which have not yet been published. It was closed before patient registration was completed because the pace of registration was slower than expected. Detailed clinical data (including laboratory data, endocrine parameters, and patient-reported outcomes) were collected, despite the small number of patients enrolled. Though the sample size was too small and not sufficient to provide for definitive conclusions, we believe that reporting these results will be useful in order to prevent publication bias and demonstrate the need for more clinical trials and/or metaanalyses to investigate the effectiveness of corticosteroids in the treatment of CRF.

METHODS

Study Design

The study was a randomized, double-blind, multicenter, placebo-controlled trial. A total of 22 institutions and hospitals participated, and the study protocol received approval from the institutional review board of each institution under the principles of the Declaration of Helsinki. All patients provided written informed consent.

Inclusion Criteria

Eligible patients were those older than 18 years of age with a diagnosis of advanced cancer confirmed on a histological or cytological examination. The other inclusion criteria were as follows: (1) the patient had a life expectancy estimated to be longer than four months; (2) there were no future plans for chemotherapy, radiotherapy, or surgical treatment; (3) patients had CRF refractory to other treatments; (4) they were able to receive medications orally; (5) patients were being treated in a hospital; and (6) they had an ALT level $\leq$300 U/ml, an aspartate aminotransferase (AST) level £300 U/ml, a creatinine level $\leq$3.0 mg/dl, and a total bilirubin level $\leq$3.0 mg/dl.

Exclusion Criteria

Patients were excluded if they (1) had severe heart disease, diabetes mellitus, active gastrointestinal ulcers, viral hepatitis, infectious disease, or tuberculosis; (2) received radiotherapy or chemotherapy in the prior four weeks; (3) had had surgery for their cancer in the previous two weeks; (4) had a history of corticosteroid allergy, (5) had been administered corticosteroids in the last two weeks, (6) required corticosteroids for other diseases; or (6) did not adequately understand their condition.

Random Allocation and Treatment

Patients were enrolled over the telephone or via fax to the data center and then randomly allocated to either a methylprednisolone (MP) group or a placebo group. Allocation of treatment groups was determined at the data center according to a dynamic randomization

method in a double-blinded manner (i.e., both patients and physicians were blinded to treatment allocation). Patients received 16 mg of methylprednisolone (32 mg/day) or placebo by oral ingestion twice daily for seven days. The type and dose of steroid employed were determined by a pilot survey from palliative care physicians from 22 institutions. All physicians preferred to use prednisolone or methylprednisolone, except for two who preferred betamethasone and one who utilized dexamethasone. The mean maximum dose of MP that physicians were using for palliative patients at that time was chosen as the intervention for the study.

Efficacy and Safety Assessments

Our primary endpoint was an improvement in patient fatigue from baseline to day 7. The secondary endpoints were improvements in appetite loss and health-related QoL. We also investigated the safety of employing corticosteroids as palliative therapy. Data regarding fatigue, appetite loss, and QoL were collected as patient-reported outcomes using a questionnaire. Degree of fatigue and appetite loss were evaluated daily according to a visual analog scale (VAS); a 100-mm horizontal line was prepared, and the patient marked on that line the point they felt represented their current state. VAS score was determined by measuring in millimeters from the lefthand end of the line to the point that the patient marked. The VAS from before drug administration (day 0) to day 8 and QoL were assessed utilizing the Questionnaire for Cancer Patients Treated with Anticancer Drugs (QoL–ACD) (Kurihara et al., 1999), the most common cancer-specific QoL scale in use in Japan, on days 0, 3, and 8.

In order to assess the safety of treatments, we performed CBC, biochemical, and endocrine examinations on days 0 and 8. In addition, the attending physician recorded the incidence of adverse events based on daily interviews, rating the level of severity on a 5-point Likert-type scale after conducting the interview and an examination—0 (none), 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe).

Statistical Analysis

The main efficacy analysis was performed based on an intention-to-treat population. The effectiveness of methylprednisolone was evaluated according to change in VAS scores for fatigue and appetite loss from baseline to day 7. Hence, the mean difference in VAS score from baseline to day 7 was compared using a t test with a 0.05 two-tailed α value between the two groups. For comparisons within groups, a paired t test was employed to compare differences from baseline to day 7.

Sample size was calculated based on an estimation of the expected effectiveness with respect to VAS score for fatigue (mean $\pm$ standard deviation):—

-40 ± 15 in the MP group and -30 ± 15 in the placebo group

—according to expected symptom improvement, with a two-tailed significant α value and statistical power set at 5 and 80%, respectively. We planned to enter 40 evaluable patients per group.

Exploratory Analysis for Future Studies

Regrettably, the pace of patient registration was insufficient to verify our primary endpoint. so we conducted the following post-hoc and exploratory evaluations in order to encourage further study. The mean difference in VAS score was compared based on daily points. For the sensitivity analysis, patients with a low baseline VAS score or poor performance status were excluded. In addition, participating physicians completed a survey immediately after the end of the study. We also investigated why patient registration was not accomplished using a questionnaire.

RESULTS

Patient Characteristics

Figure 1 presents a CONSORT flowchart of the study. We randomly assigned the 35 patients to an MP group (18 patients) and a placebo group (17 patients). One patient receiving placebo was excluded from the analysis because they withdrew consent to participate on day 1 and did not submit the questionnaire. In total, 18 patients in the MP group and 16 patients in the placebo group were included in the intention-to-treat analysis. The demographic and clinical characteristics of the two groups were not significantly different at baseline, though the number of patients with poor performance status was higher in the MP group (Table 1).

Assessment of Patients' Symptoms and QoL

As the primary endpoint, we evaluated mean difference in VAS score from baseline to day 7 (Table 2). The mean change (standard deviation) in the score for fatigue was -9.06 (27.2) in the placebo group and -1.56 (32.5) in the MP group ($p = 0.484$), while that for appetite loss was -6.44 (27.7) in the placebo group and -8.06 (38.3) in the MP group ($p = 0.892$). No significant changes were noted for either symptom. Total QoL scores at baseline and days 3 and 8 are depicted in Figure 2. A trend toward improvement in QoL score was evident in the MP group;

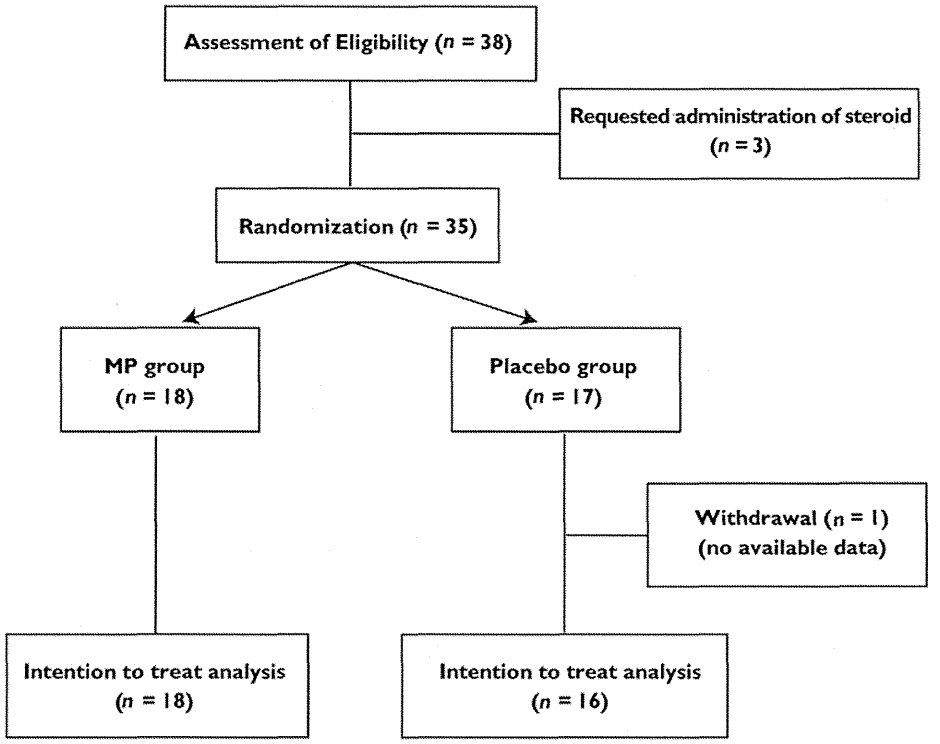

Fig. 1. CONSORT patient flowchart. Some 35 patients were randomly assigned to the methylprednisolone (MP) (18 patients) or placebo group (17 patients) from 22 participating hospitals and institutions.

however, there were no significant differences compared with the placebo group.

Laboratory Examinations

The results of comparison of the data obtained at baseline and on day 8 are shown in Table 3. The RBC, WBC, and platelet counts on day 8 were increased in the MP group. The serum AST, creatinine, bilirubin, protein, glucose, C-reactive protein (CRP), and electrolyte levels did not change significantly. Serum alanine aminotransferase (ALT) and total cholesterol levels were elevated in the MP group, though both parameters were within normal limits. There were no remarkable changes in any of the laboratory data in the placebo group.

Adverse Events

The adverse events observed during our study are given in Table 4. Six adverse events of more than grade 3 were newly detected during the observation period. One case each of diarrhea, peripheral sensory neuropathy, and dyspnea were observed in the MP group and one each of dyspnea, headache, and fever in the placebo group, though there were no significant differences between the two groups. No allergic or fetal infectious side effects were documented.

Exploratory Analysis for Future Studies

The trends in daily VAS score are shown in Figure 3. Fatigue and appetite loss improved in both groups. A certain placebo or Hawthorne effect can be assumed. However, the fatigue scores on days 5 and 6 and those for appetite loss on day 5 were relatively better in the MP group. In particular, there was a significant improvement in appetite in the MP group on day 5 ($p = 0.011$). According to our sensitivity analysis, when patients with a low performance status at baseline were excluded, the fatigue scores on days 5 and 6 and those for appetite loss on days 4 to 6 were significantly improved in the MP group. However, neither symptom differed on days 7 or 8 between groups.

Survey for Physicians Who Participated in the Study

The most common reason for delay in patient registration was that physicians hesitated in informing patients receiving palliative care about the study, though many patients in their hospital met the inclusion criteria. On the other hand, a few doctors who recruited patients found that some were quite cooperative and understood the importance of the study.

Table 1. *Patient characteristics*

	MP	%	Placebo	%	Total	%
Patients	18	100	16	100	34	100
Sex						
Male	11	61.1	10	62.5	21	61.8
Female	7	38.9	6	37.5	13	38.2
Age						
Median	71		68		69	
Range	50–84		46–84		46–84	
Primary						
Lung	7	38.9	5	31.3	12	35.3
Breast	1	5.6	1	6.3	2	5.9
Stomach	2	11.1	4	25.0	6	17.6
Colorectal	4	22.2	4	25.0	8	23.5
HBP	2	11.1	1	6.3	3	8.8
Others	2	11.1	1	6.3	3	8.8
Metastatic lesion						
None	1	5.6	1	6.3	2	5.9
Brain	3	16.7	1	6.3	4	11.8
Lung	7	38.9	4	25.0	11	32.4
Liver	3	16.7	5	31.3	8	23.5
Adrenal	1	5.6	0	0.0	1	2.9
Bone	6	33.3	9	56.3	15	44.1
Lymph node	1	5.6	4	25.0	5	14.7
Others	6	33.3	1	6.3	7	20.6
ECOG–PS						
1	2	11.1	8	50.0	10	29.4
2	6	33.3	4	25.0	10	29.4
3	8	44.4	4	25.0	12	35.3
4	2	11.1	0	0.0	2	5.9
Pretreatment						
Radiotherapy	7	38.9	9	56.3	16	47.1
Operation	11	61.1	12	75.0	23	67.6
Use of opioid	7	38.9	4	25.0	11	32.4
Antidepressant	2	11.1	3	17.8	5	14.7

MP = methylprednisolone; PS = performance status; ECOG = Eastern Cooperative Oncology Group.

DISCUSSION

The results of this trial do not demonstrate any significant differences between the MP and placebo groups in alleviating CRF. Comparisons between the two treatment arms with respect to secondary endpoints—including other patient-reported outcomes, appetite loss, and total QoL score—also uncovered no significant differences. Concerning safety, the results were acceptable regarding the use of MP in palliative treatment.

We wish to discuss the reasons why our hypothesis that corticosteroids are effective in the treatment of CRF was not proven and evaluate the difficulty in performing clinical trials focused on CRF.

First, a fatal weakness of our study was its insufficient statistical power. While the sample size estimated in the preliminary protocol was 80, only 34 patients were enrolled for the analysis. As a result, the standard deviations for all data were large, and the statistical tests were not useful. The estimation of mean VAS score was not clearly different between the two groups. However, the expected value of investigators included a 10-point advantage in calculation of sample size. Though the registration of participants was implemented successfully, there was little chance that the hypothesis could be proved in an evidenced-based manner.

Second, the problem of outcome measurements should be considered. Since "fatigue" is quite a subjective term, quantification methods for assessing it have not been established. VAS score, which was utilized in our study, has not been proven to be valid for assessing a patient's level of fatigue or appetite loss in the setting of palliative medicine. The demerits of using VAS score include the low reproducibility of measurements and larger standard deviations (Wewers & Lowe, 1990). In particular, psychological outcomes can be greatly influenced by mental or physical condition at the moment of filling out a questionnaire. When our study was conducted, there were no appropriate scales translated into Japanese that had proven validity. At the present time, there are various assessment tools for evaluating CRF, including the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire

Table 2. *The change of VAS score between day 0 and day 7*

	n	Change in VAS score	*SD*	$CI_{95\%}$	*p* Value	
Fatigue						
MP	18	−1.56	32.52	−18.89	–	15.77
Placebo	16	−9.06	27.15	−23.53	–	5.40
Difference	−7.50	–	−29.13	–	14.13	0.484
Appetite						
MP	16	−8.06	38.28	−28.46	–	12.33
Placebo	18	−6.44	27.71	−21.20	–	8.33
Difference	1.63	–	−22.50	–	25.75	0.892

MP = methylprednisolone; VAS = visual analog scale; *CI*=confidence interval.

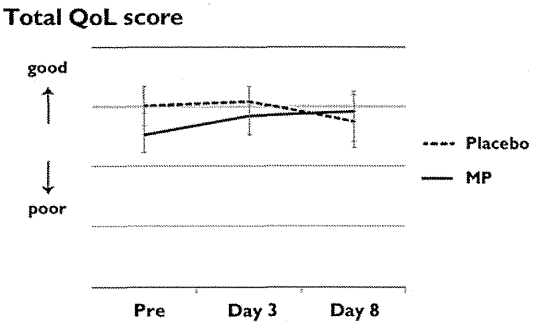

Fig. 2. Total quality-of-life (QoL) scores. Chronological changes in QoL scores and standard deviations at days 0, 3, and 8.

(EORTC–QLQ–C15–PAL) (Groenvold et al., 2006), the Edmonton Symptom Assessment System (ESAS) (Bruera et al., 1991; Chang et al., 2000), the Brief Fatigue Inventory (BFI) (Mendoza et al., 1999), and the Functional Assessment of Chronic Illness–Fatigue (FACIT–F) (FACIT.org, 2010). In a recent RCT evaluating the effectiveness of dexamethasone for CRF reported by Yennurajalingam and colleagues (2013), total FACIT–F scores on day 15 were improved in the intervention group. The FACIT–F scale contains 13 items associated with fatigue in which the patient selects one of five degrees indicating their response as it applies to the preceding seven days. Different from VAS methods, which can only be employed to evaluate symptoms at one timepoint, the FACIT–F questionnaire provides a multifaceted and more detailed assessment of the overall trend during the previous week.

Third, as a matter of course, it should be noted that the effectiveness of corticosteroids for CRF may be more limited than that assumed by many physicians. Indeed, there is little scientific evidence regarding the effects of corticosteroids on fatigue and/or appetite loss, with the RCT reported by Yennurajalingam et al. (2013) being the first clinical trial. Additionally, a large amount of dexamethasone (8 mg/day for 14 days) was administered in the present study; however, this dose is not necessarily common in palliative care patients, and information regarding the efficacy of this treatment is limited. Further studies are therefore needed to identify more effective interventions for treating CRF in palliative patients. It should also be considered that other promising interventions can be combined to enhance effectiveness, including other drugs: hematopoietic growth factors (Revicki et al., 2012) or methylphenidate (Sarhill et al., 2001); exercise (Schneider et al., 2007), and/or psychosocial interventions (Armes et al., 2007). In addition, it is important to focus on other treatable contributing factors (e.g., anemia, pain, insomnia, malnutrition, emotional distress) (Minton et al., 2010; Campos et al., 2011).

Finally, when conducting future studies, it is important for researchers to recognize the difficulty in performing clinical trials focused on patients receiving palliative care. The main reason why the pace of patient registration was delayed in our study was hesitation on the part of physicians to inform palliative care patients about the trial. Most physicians avoided registering patients, though many in their care were eligible. It is therefore necessary to recognize the importance and

Table 3. *Laboratory findings in MP group*

		Day 1	Day 8	*p* Value
RBC	$\times 10^6/\mu l$	3.21	3.59	0.002
Hemoglobin	g/dl	10.0	10.7	<0.001
WBC	$\times 10^3/\mu l$	7.2	13.7	<0.001
Neutrophils	$\times 10^3/\mu l$	5.6	11.9	<0.001
Lymphocyte	$\times 10^3/\mu l$	1.05	1.36	0.018
Platelet	$\times 10^4/\mu l$	22.4	25.3	0.066
Total bilirubin	mg/dl	0.5	0.5	0.861
AST	IU/dl	29	30	0.494
ALT	IU/dl	16	37	<0.001
Total protein	g/dl	6.1	6.2	0.791
Cholesterol	mg/dl	150	191	0.001
Glucose	mg/dl	98	100	0.725
Creatinine	mg/dl	0.7	0.65	0.124
CRP	mg/dl	3.4	1.3	0.176

MP = methylprednisolone; RBC = red blood cell; WBC = white blood cell; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CRP = C-reactive protein.

Table 4. *Adverse events*

	Total	%	MP	%	Placebo	%
Number of patients	34	100	18	100	16	100
General						
Grade ≥2	9	26.5	3	16.7	6	37.5
Grade ≤3	1	2.9	0	0.0	1	6.3
Gastrointestinal						
Grade ≥2	11	32.4	6	33.3	5	31.3
Grade ≤3	1	2.9	1	5.6	0	0.0
Respiratory						
Grade ≥2	3	8.8	3	16.7	0	0.0
Grade ≤3	2	5.9	1	5.6	1	6.3
Nervous system						
Grade ≥2	5	14.7	4	22.2	1	6.3
Grade ≤3	2	8.8	1	5.6	1	6.3
Leukocytosis						
Grade ≥2	9	26.5	7	38.9	2	12.5
Grade ≤3	0	0.0	0	0.0	0	0.0

MP = methylprednisolone.
Grade 0 (none), 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe).

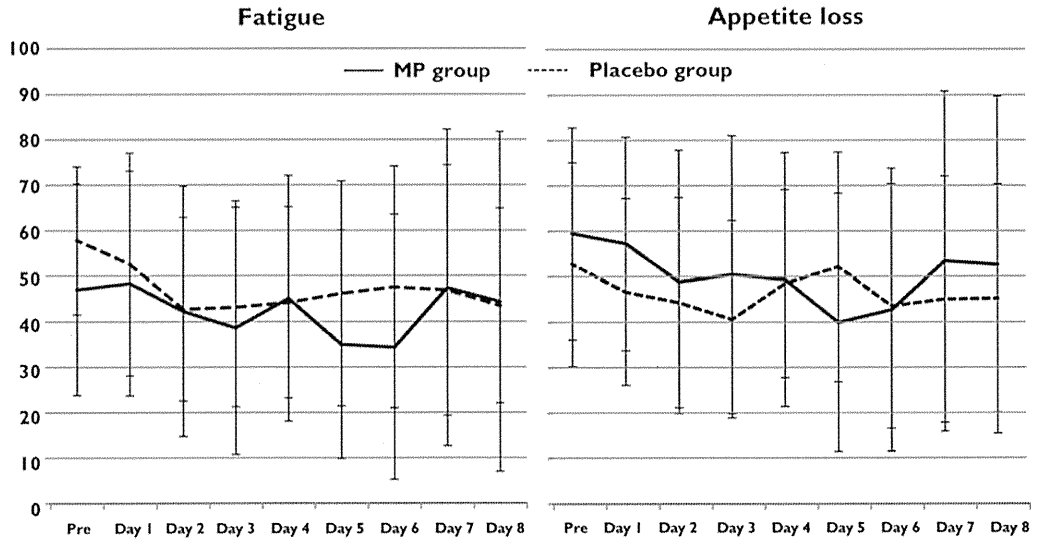

Fig. 3. Relationship among fatigue and appetite loss and visual analog scale score. Chronological changes in mean scores and standard deviations in the two groups.

need for clinical trials in order to advance palliative medicine, and investigators should be more careful in implementing a study protocol than when conducting studies outside of the palliative care milieu. Regarding informed consent, the method of obtaining informed consent should have been discussed more carefully within our study team. It is also important to prepare physicians for participation in such studies.

In conclusion, this randomized control trial was unable to prove the efficacy of methylprednisolone in improving cancer-related fatigue.

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Clinical Trial Results

A Phase I/II Study of XELIRI Plus Bevacizumab as Second-Line Chemotherapy for Japanese Patients With Metastatic Colorectal Cancer (BIX Study)

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AUTHOR SUMMARY

ABSTRACT

Background. Capecitabine is used mainly with oxaliplatin to treat metastatic colorectal cancer (mCRC). Results from capecitabine plus irinotecan (XELIRI) with or without bevacizumab (BV) have been reported in Europe but not in Japan. Consequently, the safety and efficacy of XELIRI plus BV in Japanese patients with mCRC were assessed in a single-arm phase II study.

Methods. Eligible patients had had prior chemotherapy containing BV for mCRC and wild-type or heterozygous UGT1A1. Therapy in each 21-day treatment cycle consisted of capecitabine (800 mg/m^2 twice daily on days 1–15), irinotecan (200 mg/m^2 on day 1), and BV (7.5 mg/kg on day 1). The primary endpoint was dose-limiting toxicity in phase I and progression-free survival (PFS) in phase II.

Results. A total of 34 patients (6 in phase I, 28 in phase II) were enrolled from May 2010 to June 2011. Baseline characteristics included a median age of 60 years (range: 22–74 years) for 24 men and 10 women. No dose-limiting toxicities appeared in phase I. Median PFS was 240 days (95% confidence interval: 179–311 days). Overall response rate was 18.1%, and the disease-control rate was 90.9%. The incidence of adverse events frequently associated with irinotecan and capecitabine were neutropenia (any grade, 55.9%; grade 3 or 4, 11.8%), diarrhea (any grade, 50%; grade 3 or 4, 5.9%), and hand-foot syndrome (any grade, 61.8%; grade 3 or 4, 5.9%).

Name	*NC/NA	1	2	3	4	5	All Grades
Leukocytes (total WBC)	41%	23%	35%	0%	0%	0%	58%
Neutrophils/granulocytes (ANC/AGC)	44%	8%	35%	11%	0%	0%	55%
Hemoglobin	29%	50%	17%	2%	0%	0%	70%
Platelets	52%	41%	5%	0%	0%	0%	47%
Diarrhea	50%	14%	29%	5%	0%	0%	50%
Anorexia	47%	32%	14%	5%	0%	0%	52%
Nausea	47%	32%	11%	8%	0%	0%	52%
Vomiting	70%	20%	5%	2%	0%	0%	29%
Fatigue (asthenia, lethargy, malaise)	61%	11%	23%	2%	0%	0%	38%
Mucositis/stomatitis (clinical exam)	82%	11%	5%	0%	0%	0%	17%
Dizziness	94%	0%	0%	5%	0%	0%	5%
Neuropathy: sensory	70%	17%	8%	2%	0%	0%	29%
Hair loss/alopecia (scalp or body)	67%	17%	14%	0%	0%	0%	32%
Rash: hand-foot skin reaction	38%	44%	11%	5%	0%	0%	61%
Renal/genitourinary, other	52%	20%	23%	2%	0%	0%	47%
Hypertension	67%	5%	17%	8%	0%	0%	32%

Figure 1. Adverse events during phase I/II treatment. No serious adverse events were reported.

Abbreviations: *, no change from baseline/no adverse event; AGC, absolute granulocyte count; ANC, absolute neutrophil count; WBC, white blood cells.

Conclusion. Our results suggest that XELIRI plus BV is well tolerated and effective as a second-line treatment for mCRC in Japanese patients. This regimen could be especially

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appropriate for patients resistant to oxaliplatin-based regimens. ***The Oncologist*** 2014;19:1131–1132

Discussion

In this prospective trial for Japanese patients with metastatic colorectal cancer, capecitabine plus irinotecan (XELIRI) plus bevacizumab as a second-line regimen achieved longer progression-free survival (240 days) and a higher overall response rate (18.1%) than other reported regimens, with an acceptable tolerability profile (Fig. 1). Unlike FOLFIRI, XELIRI doses do not require a long infusion process or an infuser pump, providing a great advantage to patients. The key finding in this study was that XELIRI plus bevacizumab demonstrated promising results beyond progression in Japanese patients.

Author disclosures available online.

For Further Reading:

Herbert I. Hurwitz, Niall C. Tebbutt, Fairooz Kabbinavar et al. Efficacy and Safety of Bevacizumab in Metastatic Colorectal Cancer: Pooled Analysis From Seven Randomized Controlled Trials. ***The Oncologist*** 2013;18:1004–1012.

Implications for Practice:

Several randomized trials of bevacizumab have been conducted to address specific questions regarding its use for patients with metastatic colorectal cancer (mCRC); however, because of their sample size limitations, subgroup analyses are frequently of limited power. By pooling individual patient data from seven randomized trials, more comprehensive analyses of the efficacy and safety of bevacizumab were made possible because of the large number of included patients. In addition, outcomes in clinically relevant subgroups were examined, and the data from these subgroups were consistent with those reported in the overall analyses. The results of this pooled analysis help further the clinician's understanding of the overall risks and benefits associated with adding bevacizumab to chemotherapy for patients with mCRC.

A novel system for predicting the toxicity of irinotecan based on statistical pattern recognition with *UGT1A* genotypes

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Abstract. To predict precisely severe toxicity of irinotecan, we evaluated the association of *UGT1A* variants, haplotypes and the combination of *UGT1A* genotypes to severe toxicity of irinotecan. *UGT1A1*6* (*211G>A*), *UGT1A1*28* (TA_6>TA_7), *UGT1A1*60* (*-3279T>G*), *UGT1A7* (*387T>G*), *UGT1A7* (*622T>C*), and *UGT1A9*1b* (*-118*T_9>T_{10}, also named **22*) were genotyped in 123 patients with metastatic colorectal cancer who had received irinotecan-based chemotherapy. Among the 123 patients, 73 were enrolled in either of two phase II studies of the FOLFIRI (leucovorin, 5-fluorouracil and irinotecan) regimen; these patients constituted the training population, which was used to construct the predicting system. The other 50 patients constituted the validation population; these 50 patients either had participated in a phase II study of irinotecan/5'-deoxy-5-fluorouridine or were among consecutive patients who received FOLFIRI therapy. This prediction system used sequential forward floating selection based on statistical pattern recognition using *UGT1A* genotypes, gender and age. Several *UGT1A* genotypes [*UGT1A1*6*, *UGT1A7* (*387T>G*), *UGT1A7* (*622T>C*) and *UGT1A9*1b*] were associated with the irinotecan toxicity. Among the haplotypes, haplotype-I (*UGT1A1*: -3279T, TA_6, 211G; *UGT1A7*: 387T, 622T; *UGT1A9*: T_{10}) and haplotype-II (*UGT1A1*: -3279T, TA_6, 211A; *UGT1A7*: 387G, 622C; *UGT1A9*: T_9) were also associated with irinotecan toxicity. Furthermore, our new system for predicting the risk of irinotecan toxicity was 83.9% accurate with the training population and 72.1% accurate with the validation population. Our novel prediction system using statistical pattern recognition depend on genotypes in *UGT1A*, age and gender; moreover, it showed high predictive performance even though the treatment regimens differed among the training and validation patients.

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Key words: irinotecan, polymorphisms, prediction, toxicity, uridin diphosphate-glucuronosyltransferase 1A

Introduction

Concurrent irinotecan and fluorinated-pyrimidine is a common first-line therapy for metastatic colorectal cancer (mCRC) (1-6). Although prolonged survival is associated with regimens involving irinotecan, severe neutropenia occurs in 20-35% of mCRC cases treated with irinotecan regimens. Carboxylesterases catabolized irinotecan to 7-ethyl-10-hydroxycamptothecin (SN-38), which is a potent topoisomerase I inhibitor (7,8). SN-38 is then further catabolized by hepatic uridin diphosphate-glucuronosyltransferase (UGT) 1A enzymes to an inactive SN-38 glucuronide (SN-38G) (9). Many mCRC patients with a genetic variant (*UGT1A1*28*) experience severe irinotecan toxicity; *UGT1A1*28* is a variation in the number (seven vs. six) of TA repeats in the promoter region of *UGT1A1* (10,11). Interestingly, the toxicity and tumor response of concurrent leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI) reportedly also correlate with *UGT1A* variants (*UGT1A1*, *UGT1A7* and *UGT1A9*) and haplotypes including these variants (12-18). There are differences between Caucasian and Asian populations in frequencies of *UGT1A* variants, and *UGT1A1*6* reportedly associates strongly with severe neutropenia especially among Asian patients (12,17).

To predict the risk of irinotecan toxicity for individual patients, it is important that determining the relative contributions of *UGT1A* variants other than *UGT1A1*28* and *UGT1A1*6* is important to the development of any system designed to predict irinotecan toxicity for individual patients