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Palliative Chemotherapy Preferences and Factors that Influence Patient Choice in Incurable Advanced Cancer

Min Kyoung Kim[1], Jae-Lyun Lee[2], Myung Soo Hyun[1], Young Rok Do[3], Hong Suk Song[3], Jong Gwang Kim[4], Sung Hwa Bae[5], Hun Mo Ryoo[5], Keon Uk Park[6] and Kyung Hee Lee[1]

[1]Department of Internal Medicine, Yeungnam University College of Medicine, [2]Department of Internal Medicine, Asan Medical Center, [3]Department of Internal Medicine, Keimyung University College of Medicine, [4]Department of Internal Medicine, Kyoungpook National University Hospital, [5]Department of Internal Medicine, Daegu Catholic University College of Medicine, Daegu, and [6]Department of Internal Medicine, Dongguk University College of Medicine, Gyeongju, South Korea

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Objective: To determine the extent of informed decision-making and treatment preference of Korean patients receiving palliative chemotherapy.
Methods: We assessed 138 patients (median age: 58 years; 73% male) with advanced cancer who had received at least one cycle of chemotherapy. General demographic information, the extent of information received, patient preferences for palliative chemotherapy and randomized trials were determined using structured patient interviews. We investigated the survival threshold for justifying toxicity, the factors influencing individual preference for chemotherapy and the attitude of patients towards randomized trials.
Results: Before chemotherapy, 72.1% of patients were given information about adverse events of treatment, but only 39.5% were told of alternative treatments. There was significant inter-individual variability in willingness to accept chemotherapy, as well as a wide range of thresholds. Patients reporting higher quality of life were more likely to judge treatment as acceptable. When given the choice for randomization for conventional chemotherapy, investigational agents or supportive care, patients usually refused enrollment into randomized trials.
Conclusion: Self-assessed quality of life was a significant predictor of stronger preference for chemotherapy. In the palliative setting, good doctor–patient communications and consideration of patients' preferences are necessary for making decisions about proper treatment.

Key words: palliative care – quality of life – clinical trial

INTRODUCTION

Over 50% of all cancer patients receive chemotherapy for metastatic disease (1). For individuals with incurable cancer, treatment decisions are complicated, and greater provision of information to patients, as well as their participation in treatment decision-making, is needed. Prior to choosing appropriate chemotherapy, a full discussion about treatment response, adverse events and prognosis is necessary. Several studies have suggested that, due to cultural differences, Western values about patient autonomy may not be universally applicable (2). However, most Korean cancer patients also want to be informed about their illness (3).

In Western countries, several studies focused on informed decision-making and patient preference for chemotherapy have reported that prognostic information is significantly associated with treatment choice by cancer patients (4–6). In addition, patient willingness to undergo potentially toxic chemotherapy has been found to vary widely (7–10). In Asian countries, however, relatively little is known about the decision-making processes or chemotherapy preferences of cancer patients.

Meanwhile, randomization of patients to different treatments has become accepted, almost without question, in controlled clinical trials. Nevertheless, randomization may be

For reprints and all correspondence: Kyung Hee Lee, Division of Oncology, Department of Internal Medicine, Yeungnam University College of Medicine, 317-1 Daemyung dong, Namgu, Daegu 705-717, South Korea. E-mail: lkhee@medical.yu.ac.kr

inappropriate when the clinician or patient believes that one of the treatments is superior to the other. It is not uncommon for physicians to encounter patients who refuse to participate in a randomized study. To date, there has been little research regarding the frequency or the primary reasons for refusing trial entry.

We therefore sought to evaluate the extent to which cancer patients are provided information about their disease and chemotherapy options, as well as to determine patient preference for chemotherapy and participation in randomized clinical trials.

PATIENTS AND METHODS

Patient Population

Patients participated in this study were those with metastatic solid cancers, who had received at least one cycle of chemotherapy for metastatic disease from five hospitals. Patients with education level over elementary school were included. Between March 2004 and August 2004, 138 patients were enrolled into the study along with nine oncologists at five tertiary referral hospitals. To ensure that responses were not influenced by recently experienced side effects, subjects underwent a semi-structured interview, with a trained research nurse, at least 3 weeks after previous chemotherapy. Patients were required to give written informed consent before interviews were performed. Interviews were completed by 129 patients, and their questionnaires were used in the analyses.

Interview Structure

Subjects were initially asked eight questions on sociodemographic factors, adverse events experienced during chemotherapy, improvement of symptoms and overall quality of life during chemotherapy. Sociodemographic information included age, sex, socioeconomic factors such as degree of support required and monthly income. Patients who experienced any adverse events requiring hospitalization were checked. Improvement of symptoms and quality of life were assessed using a visual analogue scale (VAS), with scores of 0–10. We classified the scores of 0–3 as poor, 4–6 as fair and 7–10 as good.

Patients were also asked four questions to assess whether they were informed about response rate, impact on survival prolongation, major adverse events and alternative treatment strategies before chemotherapy. The questions were: (i) Has your doctor told you how effective this chemotherapy has been for other patients? (ii) Has your doctor told you how long your life may be prolonged? (iii) Has your doctor told you about the major side effects? (iv) Has your doctor told you about any alternative treatments to chemotherapy?

All patients were then presented with three scenarios, each describing the same hypothetical patient, a 55-year-old man with advanced metastatic cancer who had been told by his physician that he has an incurable illness, and an expected survival without treatment of approximately 6 months. The benefits of chemotherapy were not discussed with the patients, but the purpose of clinical trials and the meaning of terms such as ‘randomization’, ‘investigational group’, and ‘control group’ were explained. The scenarios were presented in the following order, with Scenarios 1 and 2 similar to those described earlier (9):

Scenario 1: mild toxicity—in this scenario, the side effects of chemotherapy were mild and tolerated and included nausea, fatigue and asthenia, lasting several days after the treatment cycle.

Scenario 2: severe toxicity—in this scenario, the side effects of chemotherapy were sometimes severe, with a potential need for hospitalization and a 1% chance of death. The side effects included fatigue, weakness, poor appetite, mouth sores, diarrhea, infection and fever.

After each of these scenarios was presented, patients were asked the following questions: ‘Suppose that without treatment you would live 6 months. Based on your own experience of chemotherapy, would you accept this chemotherapy?’ (yes/no)

‘If you decide to receive/refuse the chemotherapy, what period of survival would make mild/severe chemotherapy-related toxicity worthwhile?’ (1/3/6/12/18/24 months)

Scenario 3: ‘At present, there are no standard treatments for your illness. The benefits of conventional chemotherapy or investigational chemotherapy with a new drug over the best supportive care have not been proven. If you were asked to participate in these three separate clinical trials, would you agree to participate?’

(i) You are randomized to conventional chemotherapy or supportive care, would you agree to participate? If not, what are your reasons for refusing?

(ii) You are randomized to conventional chemotherapy or investigational chemotherapy, would you agree to participate? If not, what are your reasons for refusing?

(iii) During the time you receive only supportive care, a new drug is developed. If your clinician advises participation in a clinical trial with the new investigational agent, would you agree to participate? If not, what are your reasons for refusing?

Each patient’s physician was asked to complete an additional questionnaire, which included diagnosis, 1st line/2nd line chemotherapy, and subjective opinion on the effectiveness of chemotherapy (poor, fair or good).

Study Analysis

The characteristics of the sample were summarized using descriptive statistics. For scenarios 1 and 2, we recorded the shortest survival duration for which each subject would choose chemotherapy. We then constructed a cumulative distribution of the percentage of subjects choosing

chemotherapy as a function of the additional survival time offered by chemotherapy. To estimate the survival threshold value for each subject, we averaged the longest survival duration for which chemotherapy was rejected with the shortest survival duration for which chemotherapy was accepted. The Paired *t*-test and χ^2-test was used to determine significant differences in variables between subgroups. Median survival thresholds across subjects were compared using the Kruskal–Wallis test for the two nominal subgroups, and the non-parametric test of trends for the two ordered subgroups. Patient and disease factors predicting individual preferences were assessed by multivariate linear regression analysis. SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA), was used for statistical computations.

RESULTS

Patient Demographics and Treatment Details

Patient characteristics are listed in Table 1. The median age was 58 years (range: 25–77 years), and the majority (72.1%) was men. During previous chemotherapy, 28 patients (21.7%) experienced moderate adverse events requiring hospitalization. Seventy-seven patients (60.7%) stated that they had some financial support from their family.

Components/Elements of Informed Decision-making

Of the 129 assessable patients, 93 (72.1%) were told about the side effects of their treatments, and 77 (59.7%) were told of responses of other patients to their chemotherapy regimens. Fewer than half, however, were given information about the impact of their chemotherapy on survival ($n = 62$, 48.1%), and just over one-third ($n = 51$, 39.5%) were presented with an alternative to anticancer therapy, such as supportive care (Fig. 1).

Patient Preferences for Chemotherapy and Trade-off Survival Threshold

Whereas 70.5% of patients agreed to receive chemotherapy with mild toxicity (Scenario 1), only 49.6% agreed to chemotherapy with severe toxicity (Scenario 2) (Table 2, $P < 0.001$). The median survival thresholds were 12 months for mild toxicity and 21 months for severe toxicity (Fig. 2 and Table 4, $P < 0.001$). No patient chose chemotherapy with severe toxicity if survival time was less than that obtained with chemotherapy with mild toxicity.

Factors Affecting Patient Preferences for Chemotherapy and Issues Potentially Associated with Trade-off Thresholds

There were significant differences in preference relative to adverse events, symptom improvement, 1st line/2nd line treatment, and self-assessed quality of life (Table 2). Multivariate analysis showed that self assessed quality of life and the oncologist's subjective opinion of the effectiveness of chemotherapy were significant predictors of stronger

Table 1. Baseline characteristics of patients ($n = 129$)

Patient characteristics	Number of patients	Percentage
Age at interview, years		
< 50	30	23.3
50–64	63	48.8
≥ 65	36	27.9
Sex		
Male	93	72.1
Female	36	27.9
Support needed from family		
None	52	40.3
Partial	71	55.0
Full	6	5.7
Monthly income, won		
< 2,000,000 (1942$[a])	96	74.4
2,000,000 ~ 4,000,000 (1942–3884$[a])	21	16.3
≥ 4,000,000 (3884$[a])	12	9.3
Adverse events experienced		
Yes	28	21.7
No	101	78.3
Symptom improvement		
Poor (0–3)	11	8.5
Fair (4–6)	39	30.2
Good (7–10)	79	61.2
Self-assessed quality of life		
Poor (0–3)	37	28.7
Fair (4–6)	55	42.6
Good (7–10)	37	28.7
Disease		
Stomach cancer	43	33.3
Colorectal cancer	22	17.1
Lung cancer	19	14.7
Pancreatic cancer	18	14.0
Esophageal cancer	9	7.0
Others	18	14.0
Chemotherapy		
1st line	97	75.2
2nd line or more	32	24.8
Physician's subjective opinion		
Good	55	42.6
Fair	59	45.7
Poor	15	11.6

[a]Converted at the exchange rate of 1029 won to the US dollar.

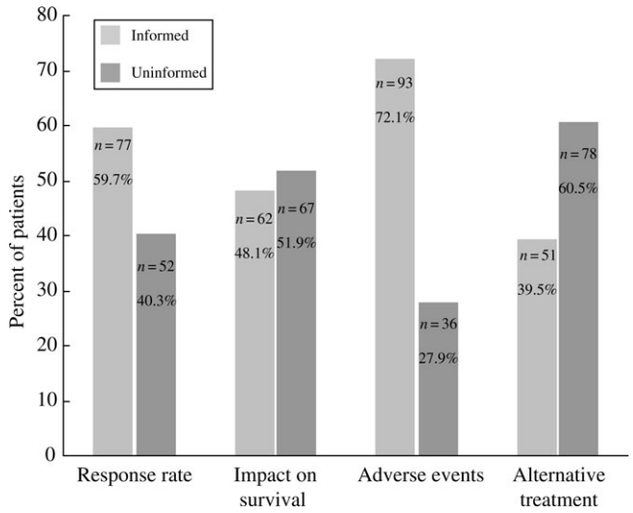

Figure 1. Patient information about their treatment ($P < 0.001$).

preference for chemotherapy, regardless of toxicity (Table 3). Age and experience of adverse events were predictors of choice of chemotherapy with severe toxicity. In contrast, other factors, including sex and socioeconomic factors, had little relationship to these thresholds. Older patients showed a trend toward being less willing to trade significant toxicity for increased survival time and their survival threshold was longer than that of younger patients (Tables 2 and 4).

Patient Preferences for Randomized Clinical Trials

A significant number of patients refused random allocation to conventional chemotherapy, best supportive care and investigational agents (Fig. 3). One hundred patients (77.5%) refused to participate in a clinical trial with randomization to a conventional chemotherapy or supportive care; of the 48 patients who provided reasons, 21 (43.8%) did so because 'chemotherapy would more likely give greater clinical benefit than supportive care', and 27 (56.2%) did so because 'the final choice of treatment has to be mine' or 'the decision should be made after discussion between patient and physician'.

In addition, 80 patients (62.0%) refused to participate in a clinical trial with randomization to conventional or investigational chemotherapy; of the 31 patients who provided reasons, 18 (58.1%) did so because 'the final choice of treatment has to be made by patients and their physicians', whereas 13 (41.9%) did so because 'I am anxious about the side effects of investigational agents'. Conversely, 75 patients (58.1%) agreed to participate in trials with investigational agents; of the 12 who provided reasons for refusal, the most common was the uncertainty of investigational agents. There were no significant correlations between sociodemographic variables and choice of trial entry.

Table 2. Response to two scenarios by patient subgroup (P values are for differences across subgroups)

Patient subgroup	Number of patients	Choice for chemotherapy			
		Scenario 1 (mild toxicity)		Scenario 2 (severe toxicity)	
		Yes	No	Yes	No
All patients	129	91	38	64	65
P value		<0.001			
Age (year)					
<50	30	21	9	21	9
50–64	63	44	19	30	33
≥65	36	26	10	13	23
P value		0.96		0.021	
Adverse events					
Yes	28	16	12	11	17
No	101	75	26	63	38
P value		0.079		0.029	
Symptom improvement					
Good	79	65	14	46	33
Fair	39	21	18	13	26
Poor	11	5	6	5	6
P value		0.001		0.038	
Quality of life					
Good	37	34	3	24	13
Fair	55	40	15	31	24
Poor	37	17	20	9	28
P value		<0.001		0.001	
1st line/2nd line					
1st line	97	75	22	55	42
≥2nd line	32	16	16	9	23
P value		0.003		0.005	
Physician's subjective opinion					
Good	55	42	13	26	29
Fair	59	45	14	37	22
Poor	15	4	11	1	14
P value		<0.001		<0.001	

Statistical significance was evaluated by χ^2 test.

DISCUSSION

In Korea, approximately 100 000 new cases of cancer are diagnosed each year, and the incidence has increased in the past 15 years (11). Up to 1980s, most Korean physicians preferred not to reveal cancer diagnoses to their patients, but in

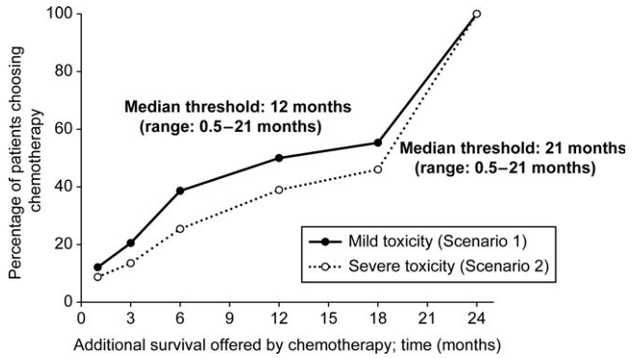

Figure 2. Cumulative distribution of the percentage of subjects choosing chemotherapy ($P < 0.001$).

Table 3. Predictors of choice for chemotherapy by logistic regression analysis

	P-value	Relative risk	95% CI
Scenario 1			
Quality of life	0.016		
Good		1	
Fair		0.58	0.21–1.63
Poor		0.16	0.04–0.71
1st line/2nd line	0.046		
1st line		1	
≥2nd line		0.39	0.15–1.00
Physician's subjective opinion	0.032		
Good		1	
Fair		0.24	0.05–1.10
Poor		0.19	0.05–0.87
Scenario 2			
Age (y)	0.031		
<50		1	
50–64		0.26	0.08–0.89
≥65		0.56	0.14–0.94
Adverse events	0.013		
Yes		1	
No		4.14	1.36–12.60
Quality of life	0.042		
Good		1	
Fair		0.27	0.08–0.96
Poor		0.51	0.17–1.51
Physician's subjective opinion	0.013		
Good		1	
Fair		0.08	0.01–0.86
Poor		0.04	0.01–0.51

CI, Confidence interval.

Table 4. Response to two scenarios by patient subgroup (P-values are for differences across subgroups)

Patient subgroup	Number (%) of patients	Median survival threshold (months)	
		Scenario 1 (mild toxicity)	Scenario 2 (severe toxicity)
All patients	129	12	21
Age (y)			
<50	30	4.5	15
50–64	63	15	21
≥65	36	15	21
P value		0.56	0.6
Symptom improvement			
Good	79	9	15
Fair	39	9	21
Poor	11	21	21
P value		0.02	0.04
Quality of life			
Good	37	9	9
Fair	55	18	21
Poor	37	21	21
P value		0.048	0.004

Statistical significance was evaluated by Kruskal–Wallis test.

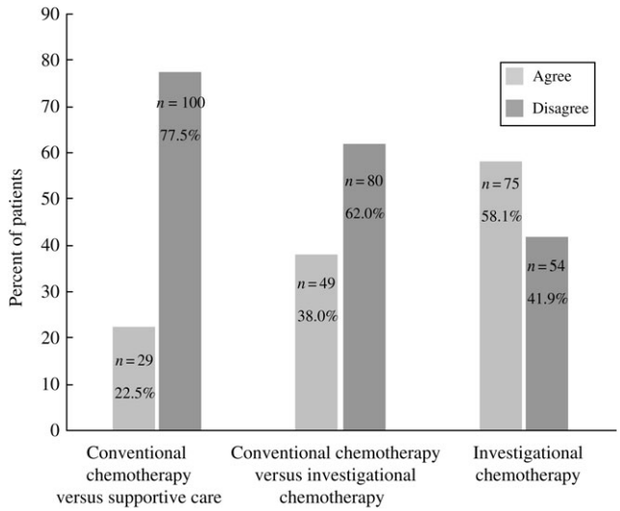

Figure 3. Responses to randomization for clinical trials ($P < 0.001$).

recent years most physicians have told their patients when they had cancer, a change that occurred approximately 20 years later than in the Western countries (12,13). We sought to evaluate the extent of informed decision-making in Korean tertiary hospitals and the expected survival time

justifying toxicity, as well as to analyze patient preferences regarding randomized clinical trials.

We found that more than 50% of patients with advanced malignancies were told of the adverse events associated with their treatment, and of the response expected. However, a minority of patients were given information about life expectancy and alternatives to anticancer therapy. Given that we assessed patient recall as a measure of informed choice, the information presented is comparable with other results (14,15). In a previous study, a significant independent effect has been demonstrated with regard to the physician's specialty, with a referral bias as patients were referred to medical oncologists for consultation about chemotherapy (16). Similarly, our finding that few patients were informed about alternative therapies shows the tendency of medical oncologists to prefer chemotherapy. It is also admitted that despite careful explanations of medical information, some patients could not comprehend these explanations or the additional factor of denial might decrease or alter receptiveness (3,17). For all events studied, our observations on informed decision-making by patients suggest that physicians supply imbalanced explanations about palliative chemotherapy, thus limiting the informed decision-making process.

Consistent with previous studies, self-assessment of quality of life had a significant relationship to the choice of chemotherapy and survival thresholds (7–10). The physician's opinion regarding chemotherapy was the other important factor. However, in contrast to previous studies, we observed no meaningful correlations between economic status and choice of chemotherapy. This may be explained in part by the availability of national insurance in Korea. In addition, there was a substantial variation in patient willingness to accept cancer treatment that was potentially toxic. A previous study showed that patients, as compared with their physicians, more commonly overestimated their chance of surviving 6 months (5). Our results show a 2-fold longer survival threshold than previous studies, and that the median survival threshold, which is often a trade-off with mild toxicity, was 12 months (9). The survival threshold was probably affected by the majority of patients overestimating their survival duration. Korean physicians have been shown to lack the time to adequately discuss clinical options, thus contributing to poor doctor–patient communication. Therefore, consideration of the time pressures on physicians should be addressed urgently to improve doctor–patient communication.

Finally, we found that most patients refused randomization to conventional chemotherapy and best supportive care, although there was no data to support one over the other. More patients consented to randomization to conventional chemotherapy or investigational chemotherapy, and 58.1% of patients agreed to investigational chemotherapy if they could choose rather than be randomized to treatment. These results are similar to those of an earlier study regarding trial-entry preferences (18). In fact, cancer patients were found to be reluctant to 'do nothing', and many patients may have mistakenly believed that 'supportive care' means 'no treatment'. One of the most contentious questions in palliative care research is whether a placebo control arm is ethically appropriate (19–21). Our results suggest a potential risk in placebo-control trials and support the importance of equipoise in the phase III setting.

Several limitations of this study should be noted. First, only patients who received chemotherapy were included in the analysis, thus possibly generating a selection bias. Second, there may be a difference between preferences in a hypothetical situation and those personally relevant in a clinical situation. In addition, we could not include all the characteristics that may influence a physician's preferences in the questions asked. For example, cost-effectiveness of therapy and patient educational level were disregarded, although they may have an impact on the decision-making process. We could not assess the reliability of the interview, and we should have used a more validated quality-of-life assessment scale. Finally, we assessed the extent of informed decision under the assumption that the majority of Korean patients preferred to be told all possible information. Further studies, on larger numbers of patients, are needed.

Despite these limitations, our findings suggest that in the palliative setting, physicians should determine patient preference for treatment and consider this aspect of patient care central to the decision regarding chemotherapy.

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Conflict of interest statement

None declared.

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