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Attitudes toward participating in Phase I clinical trials: an investigation with patient–family–physician triads

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Abstract

Objective: Phase I oncology trials have raised concerns that patients' 'unrealistic' optimism could compromise the validity of informed consent, and that patients often participate in trials to conform to physicians' or family members' recommendations. We aimed to determine whether patients or families—given the same information of risk–benefit profile—are more likely to participate in Phase I trials than their physicians and whether people in family or physician situations are more likely to recommend trial participation to patients than they would want for themselves as patients.
Methods: We conducted a hypothetical vignette study with a patient–caregiver–oncologist. Three groups—725 patient–caregiver pairs recruited by 134 oncologists—were asked to assume three different roles as patients, caregivers and physicians and provided a scenario of a hypothetical patient with treatment-resistant cancer. They were asked questions regarding their intention to participate in or to recommend a Phase I clinical trial.
Results: Acceptance rates of the trial were as follows: (a) in the patients' role: patients (54.1), caregivers (62.3) and physicians (63.4%); (b) in the caregivers' role: 55.6, 64.7 and 70.9%; (c) in the physicians' role: 66.1, 70.8 and 76.1%. Patients or caregivers were not more positive to the trial than physicians. All three groups showed more positive attitudes toward the clinical trial when they assumed the role of caregiver or physician than that of patient.
Conclusions: Patients and caregivers seem to make as reasonable decisions as physicians; patients seem to take family members' or physicians' recommendation as their legitimate roles rather than as undue pressure.

Key words: Phase I clinical trial, cancer, oncology, attitudes

Introduction

Despite improvement in treatment and medical technologies, over 7.6 million people diagnosed with cancer die from it annually. Research finding novel therapies for cancers remains an important health priority. Phase I clinical trials are crucial for developing new anticancer therapeutic agents. Yet, given that patients are physically and emotionally vulnerable, ethical issues remain unsolved and controversial regarding patients' decision-making process to participate in Phase I oncology trials.

The validity of informed consent is one of the most common issues of Phase I trials. The proportion of patients who experience clinical benefit from a Phase I trial is generally low, and many experience toxicity (1). However, there are also dramatic examples of success cases such as the medication 'imatinib mesylate' (1,2); patients experience dilemma with this uncertainty of clinical outcomes. Patients offered Phase I trial participation express higher optimistic expectations of personal benefit (e.g. >50%) than actually occurs in the historical data (5%) (3). There is concern that such 'unrealistic' optimism could compromise the validity of informed consent (4), suggesting that patients with fair understanding of benefit–risk ratios would not participate in Phase I trials (5). Such high expectation of benefits in Phase I trials would be an expression of hope rather than a misunderstanding of benefit–risk ratio (1,6,7). Yet, it is not clear how much a misunderstanding or expression of hope contributes to patients' choices. It is difficult to determine reasonableness of patients' choices without a gold standard for definition of favorable risk–benefit ratio and reasonable choices that well-informed patients would make (1,8). Considering that physicians would have the most 'realistic' expectation of benefits–risks of a new therapeutic agent, it would be helpful to examine physicians' choices, assuming that they were the patients who were asked to participate in a Phase I clinical trial (3).

Another issue regarding Phase I trials is the voluntariness of patient participation. One of the most influential factors is physician's recommendations (9,10). Some patients want doctors to recommend treatments that they would need to follow (11). Conversely, some patients participate because they cannot refuse a doctor's recommendations (12,13). Family members also play an important role in the decision-making process of clinical trial participation (10,14). The decision is often made by family council (9,15); some patients took their family's decision to maintain relationships with their loved ones (12,16). Such findings related to voluntariness raise concerns about patients' autonomy and best interests; however, we do not know whether patients take physicians' or family members' recommendations regarding Phase I trial participation as coercion.

To address the above concerns and expand our understanding of the context of the decision-making process of Phase I oncology trials, we conducted a hypothetical vignette study with a patient–caregiver–oncologist triad to determine the following: (1) whether patients or families—given the same information of risk–benefit profile—are more likely to participate in Phase I trials than their physicians, (2) whether people in family or physician situations are more likely to recommend trial participation to patients than they would want for themselves as patients and (3) to what extent physicians' opinions concur with patients' or families' opinion.

Patients and methods

Study design and subjects

This study was performed as part of the CaPE (Cancer Patient Experience) Study, the fifth annual national survey on cancer patients' experience to develop comprehensive supportive care in Korea. In 2012, the survey examined matched physician–patient–caregiver triads to explore and compare their views on medical care. The study was funded by the Ministry of Health and Welfare, and the National Cancer Center and 12 government-designated Regional Cancer Centers participated in the survey. The study was approved by the Institutional Review Board of the National Cancer Center.

We selected ~10 board-certified oncologists in each center. Each oncologist was asked to recruit five consecutive patients and their caregivers. Inclusion criteria for patients were: (1) older than 18 years, (2) histologically confirmed with cancer, (3) currently receiving cancer treatment or follow-up care and (4) physically and mentally able to complete the study questionnaires. Caregivers older than 18 years were recruited. Patient–caregiver dyads were enrolled when both a patient and a family member agreed to participate.

Of 144 oncologists invited, 134 (93%) agreed to participate and completed the survey according to the instructions. The oncologists provided a brief overview of the study to eligible patients and caregivers and asked whether they were willing to participate. Upon agreement of both patient and caregivers, trained research coordinators explained details of the study and obtained informed consent. Among 960 patients and caregivers invited, 725 dyads agreed to participate and completed the survey (75.5% participation rate). Consenting patients and family members were instructed to independently complete the study questionnaires in a separate area to avoid consultation or sharing of information. Physicians were instructed to complete the survey for each patient soon after seeing the patient. Oncologists recruited six patients on average (with a range of 1–15 dyads).

Measures

To answer the research questions, we developed a scenario in which a hypothetical patient (Mr Kim)—diagnosed with pancreatic cancer 1 year ago—received two regimens of chemotherapy, no proven therapy was available and needs to decide whether to participate in a Phase I clinical trial for a potentially promising chemotherapeutic agent (Supplementary Text). Based on the literature regarding the efficacy and side effects of previous Phase I chemotherapeutic agents (2,17), we detailed the expected tumor responses along with probabilities, expected clinical benefits and potential serious adverse effects. We used frequency-type probability statements because they are the most appropriate for conveying objective knowledge of the trial in a way that participants could comprehend (6,18). To prevent negative connotations of the term 'no therapy' and to protect from suggestions of coercion, enrollment in a palliative care program for pain and symptom management was offered provided as an alternative to participation in the trial (19–21).

After seeing the scenario, the same questions assuming three different roles in the clinical encounter were asked of patients,

caregivers and physicians: (1) If you are Mr. Kim, would you participate in the clinical trial? (2) If you are Mr Kim's family caregiver, would you recommend that he participate in the trial? (3) If you are Mr. Kim's physician, would you recommend that he participate in the trial? Response options were binary (Yes/No).

Patients, caregivers and physicians were also asked to provide their sociodemographic information. Clinical information for the patients was retrieved from hospital information systems at the participating centers: primary cancer diagnosis, Surveillance, Epidemiology, and End Results (SEER) stage and time since cancer diagnosis.

Statistical analysis

Summary statistics were computed for all variables for each group. Their responses to each hypothetical scenario for Phase I trial participation were cross-tabulated and compared with responses in their current roles using McNemar or chi-square tests, as appropriate. Percentage agreement and kappa statistics were examined for concordances between the groups. We additionally explored the factors determining the attitudes toward Phase I trial participation in each group. All statistical analyses were conducted using STATA version 12.0 (StataCorp., TX); *P*-value <0.05 was considered statistically significant.

Results

Subject characteristics

Sociodemographic and health status characteristics of study participants are shown in Table 1. Patients averaged 60.2 years of age and were more likely to be female (54.6%). The majority (84.9%) were

Table 1. Characteristics of patient–caregiver dyads (*N* = 725)

Patient Characteristics (*N* = 725)	*N*	%	Caregiver Characteristics (*N* = 725)	*N*	%
Age	60.2	12.5	Age	51.3	13.4
Gender					
Male	329	45.4	Male	310	42.8
Female	396	54.6	Female	415	57.2
Marital status			Marital status		
Married	615	84.9	Married	612	84.5
Unmarried	109	15.0	Unmarried	112	15.5
Educational status			Educational status		
<9 years	345	47.6	<9 years	200	27.6
9–12 years	236	32.6	9–12 years	256	35.3
>12 years	139	19.2	>12 years	266	36.7
Missing	5	0.7	Missing	3	0.4
Religion			Religion		
None	277	38.2	None	289	39.9
Christian	146	20.1	Christian	144	19.9
Catholic	55	7.0	Catholic	60	8.3
Buddhism	225	31.0	Buddhism	208	28.7
Others	18	2.5	Others	21	2.9
Missing	4	0.6	Missing	3	0.4
Income (KRW)*			Income (KRW)		
<2 million	423	58.3	<2 million	292	40.3
≥2 million	293	40.4	≥2 million	420	57.9
Missing	9	1.2	Missing	13	1.8
Cancer type, primary cancer			Relationship to patients		
Stomach	118	16.3	Spouse	437	60.3
Lung	98	13.5	Adult child	207	28.6
Liver	52	7.2	Parents	39	5.4
Colon	130	17.9	Others	42	5.8
Breast	103	14.2	Caregiving duration		
Cervix	50	6.9	Mean, SD	2.3	3.3
Others	174	24.0	<1 year	200	27.6
SEER stage (current)			1–2 years	201	27.7
In situ and local	261	36.0	> 2 years	305	42.1
Regional	230	31.7	Missing	19	2.6
Distant	223	30.8	Average caregiving hours/week		
Unknown/missing	14	1.9	≤5 hours/week	283	39.0
Treatment status			5–20 hours/week	140	19.3
Under initial treatment	324	44.7	20–40 hours/week	59	8.2
On regular follow-up after initial treatment	237	32.7	Almost always	234	32.3
On regular follow-up after cure	39	5.4	Missing	9	1.2
Under treatment for metastasis or recurrence	107	14.8	Living with patients	234	32.3
Don't know	14	0.4	Yes	535	73.8
Others (e.g. treatment for second cancer)	3	0.1	No	190	26.2

*KRW: Korean Won; average monthly wage in Korea was 2903 USD or 3500 KRW in 2009 by International Labour Organization statistics.

married; 58.3% reported an income of <2 million KRW. Slightly fewer than half (47.6%) had less than a high school education. Colorectal, stomach, breast and lung cancer were the most common diagnoses; the majority of patients (44.7%) were in an initial treatment phase or regular follow-up after treatment (32.7%). Disease stage was evenly distributed among local (36.0%), regional (31.7%) and distant/metastatic (30.8%). Family caregivers were somewhat younger, better educated, more likely to be female and more financially secure than the patients. Most of the caregivers were spouses (60.3%) and adult children (28.6%; Table 1). Physicians were predominantly male (79.9%); half were surgical oncologists (50.8%; Table 2).

Responses according to hypothetical roles

The acceptance rates of the trial in the patient role were patients (54.1), caregivers (62.3) and physicians (63.4%). The proportion of patients, caregivers and physicians who would recommend the trial in caregivers' role were 55.6, 64.7 and 70.9% respectively; those in the physicians' role were 66.1, 70.8 and 76.1%, respectively. Overall, family caregivers were slightly more positive than the patients about Phase I trial participation regardless of their hypothetical roles, but the absolute differences was small (<10%). Physicians showed a similar trend but were not statistically significant (Fig. 1).

Some participants changed their responses according to their hypothetical roles. All three groups of respondents showed more positive attitudes toward the clinical trial when they assumed the role of a caregiver than that of a patient and when they assumed the role of a physician than a caregiver (Fig. 2). While most changes occurred in such direction, a minority of patients changed their stance in the opposite direction (Supplementary data, Table S1).

Table 2. Characteristics of oncologists ($N = 134$)

Physician Characteristics ($N = 134$)	N	%
Age (mean, SD)	43.5	7.8
Gender		
Male	107	79.9
Female	27	20.1
Specialty		
Medical oncologist	59	44.0
Surgical oncologist	68	50.8
Radiotherapy oncologist	7	5.2
Years after board certification		
Mean, SD	12.3	7.5

SD, standard deviation.

Concordance of responses in the current role

Considering the matched triad design, we examined concordances of respondents' responses assuming the patient was Mr Kim, the caregiver was Mr Kim's caregiver and the physician was Mr Kim's physician. Agreement between patient and caregiver occurred in 64.7% of pairs, but the level of concordance was low (Kappa = 0.252, $P < 0.001$). Agreement between patient and physician occurred in 56.0% of pairs; agreement rate between caregiver and physician was 61.1%. The level of concordance was very poor with Kappa values of 0.023 and 0.026, indicating no better than chance agreement (Table 3).

Factors determining the attitudes in each group

Female patients were less likely to accept the Phase I trial in the patients' role (odds ratio (OR) = 0.563; 95% confidence interval (CI), 0.397–0.797) or in the caregivers' role (OR = 0.644, 95% CI, 0.451–0.919). Older caregivers were slightly more likely to accept the trail in the patients' or caregivers' role (OR = 1.002; 95% CI, 1.000–1.003, for both roles). Surgical oncologist were less likely to recommend the trial in caregivers' (OR = 0.418; 95% CI, 0.185–0.945) or physicians' role (OR = 0.224; 95% CI, 0.086–0.584) (Supplementary data, Table S2).

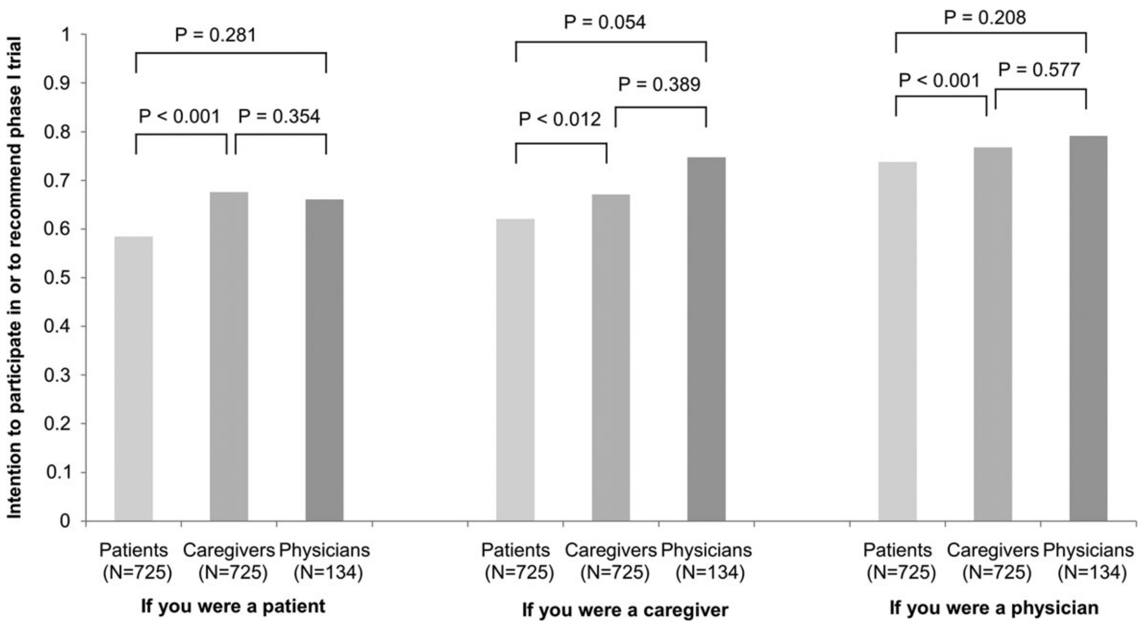

Figure 1. Patients', caregivers' and physicians' intention to participate in or recommend Phase I clinical trial in hypothetical situations. *P*-value: by McNemar test (for patient–caregiver comparison); by chi-square test (for patient–physician and caregiver–physician comparisons).

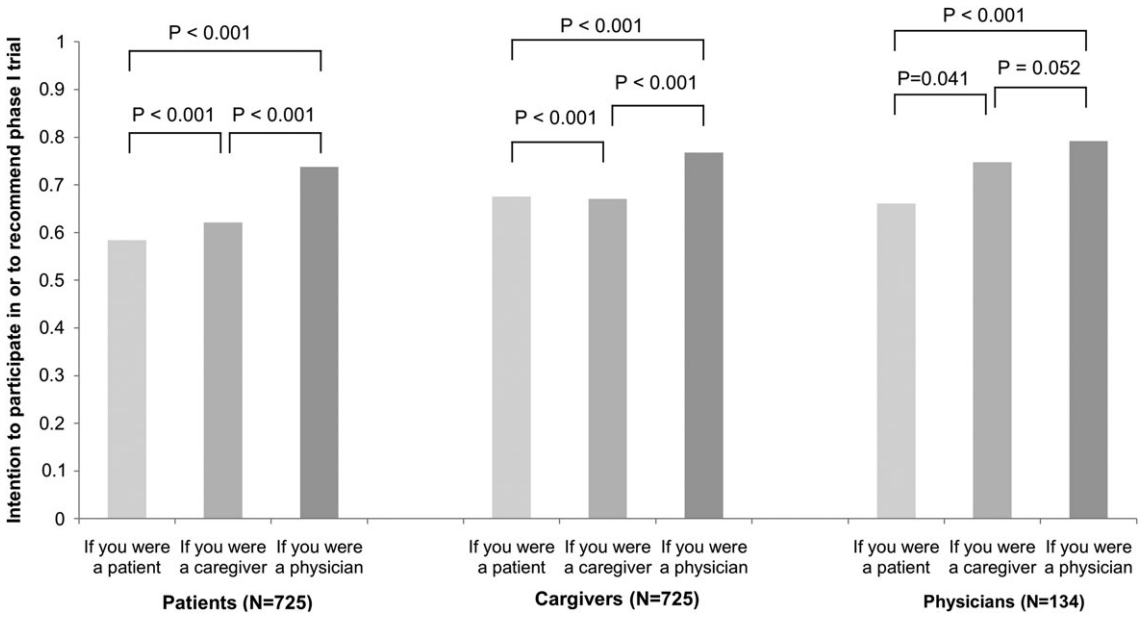

Figure 2. Changes of intention to participate in or recommend Phase I clinical trial in hypothetical situations. *P*-value: by McNemar test (for patient–caregiver comparison).

Table 3. Concordances of intention to participate in or recommend clinical trial between patients, caregivers and physicians

	Caregiver			Concordance		
Patient	Yes	No	Missing	Agreement (%)	Kappa	*P*-value
Yes	302	87	1	64.7	0.252	<0.001
No	148	130	3			
Missing	13	19	22			
	Physician			Concordance		
Patient	Yes	No	Missing	Agreement (%)	Kappa	*P*-value
Yes	316	76	0	56.0	0.023	0.251
No	219	60	0			
Missing	15	39	0			
	Physician			Concordance		
Caregiver	Yes	No	Missing	Agreement (%)	Kappa	*P*-value
Yes	376	93	0	61.1	0.026	0.236
No	179	51	0			
Missing	7	19	0			

Discussion

Communication between patients, family caregivers and oncologists is crucial for patients to participate in trials. To the best of our knowledge, this is the first study to examine such communication in patient–caregiver–physician triads with a large population. Our study showed that most patients and caregivers did not overestimate the benefits of a trial than physicians. Patients were more likely to recommend trial participation when assuming caregiver and physician roles than being patients; physician responses did not concur with those of patients or caregivers.

In previous studies, there was concern that patients participating in Phase I trials would have limited understanding of trial purpose and overestimate benefits of the trial (19). We found that patients' or caregivers' willingness to participate were not higher than those of physicians in the same situation of being a hypothetical patient. This suggests that assuming that physicians would make the most 'realistic' or 'rational' choice, patients and caregivers seemed also make 'realistic' decisions with appropriate information. Although physicians often underestimated patients' ability to make decisions regarding trial participation, studies report that most patients entering Phase I trials feel that they were adequately informed about the purpose of the study, understood risks–benefits and had confidence making informed decisions (22).

Alternative interpretation for such similar responses between patients and physicians would be that even physicians could make 'unreasonable' decisions when facing challenging situations. Research suggests that people, including physicians, fail to construct their personal beliefs in accordance with probability theory (18). Given that most patients enrolled in trials understand the purposes correctly, the uncertainty of clinical outcomes, low likelihood of historical benefits (12,22), and expression of high expectations were interpreted as therapeutic optimism rather than therapeutic misconception or misestimation (5,12,23,24). Patients and physicians facing inevitable death might know that the chance of having benefits is low but still maintain hope that their own chance of getting therapeutic benefits is high (24,25).

Our study showed that physicians and family caregivers would recommend patients participate in a trial more than they would participate themselves. A Chinese study had similar findings: 64.4% of oncologists would recommend their patients participate in Phase I trial but only 48.2% of them would be willing to participate in the trial if they were a patient (26). This reflects that some physicians and caregivers recommend a trial that they would not participate in if they were patients. Given that physician recommendations (27) and family will (16) are the most important reasons for patients to participate in a cancer clinical trial, such a double standard may raise concern about a downfall of patients' autonomy and best interest for patients. This would be more problematic in non-Western cultures where medical paternalism is prevalent and family decision-making is more common (11,14,27).

However, caregivers and physicians may perceive that it is their role to encourage patients to participate in trials even with small benefits. In our study, patients also said that they would more recommend trial participation to the hypothetical patient if they were physicians or family members. Similar observation was found in a Canadian study: people chose more intensive treatment for a hypothetical patient facing a life-threatening situation when they assumed the role of family member or treating physician than when they assumed themselves as patient (28). Family or physicians often recommend a trial with good intentions to make patients feel cared for and encourage them to try whatever they want. Patients actually appreciate such encouraging environment and do not consider it a threat to their best interest or autonomous decision (5). Further empirical studies with a perspective of relational autonomy (29) are necessary to clarify dynamics of communication among patients, caregivers and physicians in a real setting.

We found concordance of responses between patients and physicians and between family caregivers and physicians regarding participation in trials was not higher than chance agreement. Similar findings were observed with family and physicians' acceptance of using novel anticancer agents with limited efficacy for terminal cancer patients (30). Physicians are known to be poor at predicting the needs and preferences of patients (31). Nobody, including physicians, can make better decisions in terms of participation in clinical trials (32,33). If physicians do not inform a patient about an available Phase I trial based on their own estimation of benefit–risk ratio, it could be an undue deprivation of opportunity for patients who might want to participate in the trial.

In our study, male patients and older caregivers were more likely to accept Phase I trial in patients' or caregivers' role. This is consistent with the result of systematic review on the attitudes towards participation in cancer clinical trial (34). Interestingly, surgical oncologists were less positive in recommending the trial participation in caregivers' or physicians' role. This also concurs with the previous finding that physicians value more on prolonging a patient's life and are more active in recruiting patients in cancer clinical trial than surgeons (35).

Several limitations of the study should be noted. First, our work relied on a hypothetical scenario. A choice made in an assumed situation may not be equivalent to actual decisions made in real-life circumstances (26), and may not capture the process aspect of communication in which patient, caregiver and physician interact. Standardized situations, however, help respondents make objective decisions regarding risk–benefit ratios; we could explore respondents' preferences according to the assumed role as patient, family caregiver or physician. Moreover, patients in a real situation tend to avoid this kind of topic; many would refuse to participate in the survey (36). A clinical vignette approach is often the only method to standardize the situation for investigation of preferences and decision making (13) and, therefore, has been widely used to provide valuable insight for clinical practice (10,28,37,38). Although we have not formally test the validity of our clinical vignettes especially in low education people, the use of single brief and simple case and non-significant difference according to educational status (Supplementary data, Table S2) suggest that the effect of education status on the validity of our clinical vignette might not be large. Second, family caregivers who participated in this survey might not be representative of all family members; however, the family member is likely to be the closest caregiver who shared the illness experience and would usually be the most influential person in the trial participation within the family. Finally, generalizability outside of the Korean culture needs to be examined as family communication regarding clinical trial participation is likely to be influenced by cultural context (9). However, we believe our study also provides unique insight to the communicational aspect in Asian population, who generally value less on the patient autonomy and more on the family harmony.

Our study does not address all questions surrounding communications regarding Phase I trial participation among patients, family and physicians; however, it has important implications from clinical and ethical perspectives. Considering that patients and family caregivers can make reasonable decisions as much as physicians, we should provide patients accurate, objective risk–benefit information about Phase I trials. Because patients can take family members' or physicians' recommendations as their legitimate roles rather than as undue pressure, oncologists involved in Phase I clinical trials should encourage communication between patients, caregivers and physicians. Finally, information on the availability of relevant Phase I clinical trials should be provided regardless of physician's individual preference.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

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Conflict of interest statement

None declared.

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