

Complementary/Alternative Medicine Experience in Cancer Patients: A Questionnaire-Based Survey

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ABSTRACT

A study was designed to evaluate the frequency of complementary/alternative therapy (CAM) knowledge and usage in cancer patients. A 23-item survey questionnaire was administered to 494 patients who received chemotherapy in the medical oncology department of three hospitals between June 2011 and December 2011. After giving written informed consent, patients completed a self-administered questionnaire. Differences among participants were assessed by using the SPSS 17.0 software. Of the 494 patients, 48% had heard of CAM, and 23.5% had used at least one CAM model. Herbs and vitamins were the most frequently used approach (82.2%). The most commonly used herb was the stinging nettle (55.5%). Marital status ($p=0.003$), educational status ($p<0.001$), monthly income ($p<0.001$), knowledge about disease ($p<0.001$), family history of comorbidity ($p<0.012$), and place of residence (0.004) were statistically significant for knowledge about CAM. However, marital status ($p<0.001$), comorbidity ($p=0.004$), educational status ($p=0.006$), family history of comorbidity ($p=0.008$), and family history of cancer ($p=0.03$) were statistically significant for CAM use. Logistic regression analysis showed that educational status ($p=0.015$), high monthly income ($p=0.03$), knowledge about disease ($p=0.005$), and a family history of comorbidity ($p=0.005$) were statistically significant for knowledge about CAM. Otherwise, only marital status ($p<0.001$) and comorbidity ($p=0.04$) were determined as independent factors for CAM use. Health professionals should routinely ask their patients about CAM use and discuss the reasons and outcomes of use. Randomized clinical trials are needed to determine possible risks and benefits associated with CAM use.

Keywords: Cancer, Complementary and alternative medicine

ÖZET

Kanser Hastalarında Tamamlayıcı/Alternatif Tedavi: Bir Anket Çalışması

Kanser hastalarında tamamlayıcı/alternatif tedaviyi (TAT) bilme ve kullanma sıklığını değerlendirmek için bu çalışma dizayn edildi. Haziran 2011 ile aralık 2011 tarihleri arasında, 3 hastanenin medikal onkoloji departmanında tedavi gören toplam 494 hastaya 23 soruluk bir anket uygulandı. Hastalara yazılı bilgilendirilmiş onam formu imzalatıldıktan sonra, kendilerinin doldurması için anket formları verildi. Katılımcılar arasındaki farklar SPSS.17 paket programıyla değerlendirildi. Toplam 494 hastanın %48'i TAT terimini duymuş, %23.5'i de en az bir TAT modelini kullanmıştı. Bitkiler ve vitaminler en sık kullanılan yaklaşımdı (%82.2). En sık kullanılan bitki ise ısırgan otuydu (%55.5). Medeni durum ($p=0.003$), eğitim durumu ($p<0.001$), aylık gelir düzeyi ($p<0.001$), hastalığı bilme durumu ($p<0.001$), ailede komorbidite varlığı ($p<0.012$) ve yaşadığı yer ($p=0.004$), TAT hakkında bilgi sahibi olma durumuyla istatistiksel olarak anlamlı bulundu.

Bununla beraber, TAT kullanımıyla medeni durum ($p < 0.001$), ek hastalık varlığı ($p = 0.004$), eğitim durumu ($p = 0.006$), ailede komorbidite varlığı ($p = 0.008$) ve ailede kanser varlığı ($p = 0.03$) istatistiksel olarak anlamlı bulundu. Lojistik regresyon analizi yapıldığında ise, eğitim durumu ($p = 0.015$), yüksek aylık gelir düzeyi ($p = 0.03$), hastalık hakkında bilgi sahibi olma durumu ($p = 0.005$), ailede komorbidite varlığı ($p = 0.005$) TAT hakkında bilgi sahibi olma durumuyla ilişkili idi. Sadece, medeni durum ($p < 0.001$) ve komorbidite varlığı ($p = 0.04$) TAT kullanımıyla ilişkili olan bağımsız faktörler olarak saptandı. Sağlık çalışanları, rutin olarak hastalarına TAT kullanımını sormalı ve sebepleriyle kullanımdan kaynaklanabilecek sonuçları tartışmalıdır. TAT kullanımının olası risk ve faydalarını saptamaya yönelik randomize çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Kanser, Tamamlayıcı/alternatif tedavi

INTRODUCTION

Patients diagnosed with cancer have many different problems. Currently, many types of cancer can be treated successfully. Unfortunately, some advanced stage cancers are managed only with palliation. If patients decide to be treated with modern oncological therapy, some side effects and treatment failure will likely develop. Then, patients can feel as though they have no options left. At this point, the use of complementary and alternative medicine (CAM) becomes a part of therapy.

As defined by the National Center for Complementary and Alternative Medicine (NCCAM), CAM includes “a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine”.¹ This term may be included in two different meanings. One of them is “complementary medicine,” which describes the use of CAM in concurrence with conventional medicine, while the other term is “alternative medicine” and refers to the use of therapies in place of conventional medicine.

Usually, cancer patients use complementary and alternative medicine in addition to modern medicine. Among cancer patients, CAM is considered as natural, non-toxic, and has health promoting effects.^{2,3} Therefore, CAM is very popular among cancer patients and gives them hope for a cure. In addition, these patients want to try all therapies other than modern therapies.

CAM includes a wide range of methods and therapy categories. According to the National Center for Complementary and Alternative Medicine, CAM therapies classify into four categories¹:

1. Natural products and supplements, such as herbal medicines (botanicals), vitamins, and minerals
2. Mind-body interventions like meditation, yoga, acupuncture, prayer, mind and body practices (deep-breathing exercises, hypnotherapy, progressive relaxation, qi gong)

3. Manipulations and body-based methods like chiropractic, osteopathic manipulation, and massage

4. Others such as energy therapies (magnet therapy, light therapy, qi gong, Reiki, healing touch) and alternative medical systems, including traditional Chinese Medicine and Ayurveda etc.

Medical traditional methods in Turkey date back to ancient times in Anatolia, also known as Asia Minor.⁴ CAM is practiced almost exclusively by people who are not educated in conventional medicine. CAM practices cover a wide spectrum, ranging from herbal prescriptions, religious practices such as “muska (script writing)” or “ufleme (touch and pay),” to “old woman medicine” practices such as drinking turtle blood or eating the flesh of a mole (Talpidae).⁵ Institutions called “Ocak” in Turkish, where a form of CAM is practiced to cure a multitude of diseases, fractures, and dislocations, exist at numerous locations in Anatolia. A sort of alternative medical practitioner called “Ocaklı” (folk physicians) perform CAM functions in these places. CAM also involves therapy through nonconventional drugs, which are mostly of herbal origin and at times animal or inorganic.⁵ However, medical practice in Turkey is modern medicine.

It is important to know the types of CAM that cancer patients are using. Some of these modalities/therapies have important toxicities and can be dangerous in combination with chemotherapy. Therefore, a questionnaire-based survey was performed to understand frequency, knowledge, and demographics of CAM usage in our cancer patients.

METHODS

Patient Population and Procedures: This study was conducted on adult (18 years of age or older) patients diagnosed with cancer who attended ambulatory patient care units at the three hospitals in their Department of Medical Oncology, from June 2011 to December 2011. Patients who were too ill (performance status) to complete the interview were excluded. The

Table 1. Sociodemographic Characteristics of patients who had knowledge about CAM or not.

Characteristics	Yes, n (%)	No, n (%)	Total, n (%)	p
Age				
<40	17 (44.7)	21 (55.3)	38 (100)	0.09
40-50	45 (55.6)	36 (44.4)	81 (100)	
50-60	79 (56.4)	61 (43.6)	140 (100)	
60	96 (44.4)	120 (55.6)	216 (100)	
Gender				
Female	125 (50.4)	123 (49.6)	248 (100)	0.81
Male	112 (49.3)	115 (50.7)	227 (100)	
Marital Status				
Married	208 (51.9)	193 (48.1)	136 (100)	0.003*
Single	5 (18.5)	22 (81.5)	27 (100)	
Divorced	24 (52.2)	22 (50)	474(100)	
Place of residence				
Urban	130 (57)	98 (43)	228(100)	0.004*
Rural	106 (43.6)	137 (56.4)	243 (100)	
Educational status				
Illiterate	13 (44.8)	16 (55.2)	29 (100)	<0.001*
Primary school	138 (43.9)	176 (56.1)	314 (100)	
Junior high school	17 (48.6)	18 (51.6)	35 (100)	
High School	34 (63.0)	20 (37.0)	54 (100)	
University	35 (81.4)	8 (18.6)	43 (100)	
Insurance				
Medicare for civil servant	68 (50)	68(50)	136 (100)	0.98
Medicare for worker	147 (50.2)	146 (49.8)	293 (100)	
Private	4 (57.1)	3 (42.9)	7 (100)	
Other	17 (51.5)	16 (48.5)	33 (100)	
Profession				
Housewife	93 (45.8)	110 (54.2)	203 (100)	0.25
Worker	15 (50)	15 (50)	30 (100)	
Self-employed	20 (57.1)	15 (42.9)	35 (100)	
Farmer	17 (41.5)	24 (58.5)	41 (100)	
Civil servant	60 (58.8)	42 (41.2)	102 (100)	
Retired	32 (50.8)	31 (49.2)	63 (100)	
Comorbidity				
Yes	77 (47)	87 (53)	164 (100)	0.33
No	158 (51.6)	148 (48.4)	306 (100)	
Family history of comorbidity				
Yes	114 (56.4)	88 (43.6)	202 (100)	0.012*
No	120 (44.8)	148 (55.2)	268 (100)	
Family history of cancer				
Yes	78 (52.0)	72 (48.0)	150 (100)	0.53
No	158 (48.9)	165 (51.1)	323 (100)	
Knowledge about disease				
Yes	223 (53.5)	194 (46.5)	417 (100)	<0.001*
No	9 (20.5)	35 (79.5)	44 (100)	
Monthly income				
<MW	42 (35.9)	75 (64.1)	117 (100)	<0.001*
MW up to 2 times MW	146 (53.3)	128 (46.7)	274 (100)	
>2 times MW	26 (81.3)	6 (18.8)	32 (100)	
Social relief	19 (44.2)	24 855.8)	43 (100)	

MW: minimum wage; *: p significant

questionnaires were handed out to the patients by their nurses on arrival at the hospital as outpatients. Informed consent was obtained from all patients. It was explained to the patients that all information offered would be treated confidentially, and that refusal

to participate in the study would not jeopardize their care in any way.

Questionnaire: The questionnaire was in Turkish and consisted of 23 questions. Most of them were multiple-choice questions; however, the patients were

Table 2. Sociodemographic Characteristics of patients who had used or not CAM

Characteristics	Yes, n (%)	No, n (%)	Total, n (%)	p
Age				
<40	11 (30.6)	25 (69.4)	36 (100)	0.83
40-50	18 (22.8)	61 (77.2)	79 (100)	
50-60	35 (25.4)	103 (74.6)	138 (100)	
60	52 (24.3)	162 (75.7)	216 (100)	
Gender				
Female	59 (24.7)	180 (75.3)	239 (100)	0.93
Male	57 (25.0)	171 (75.0)	228 (100)	
Marital Status				
Married	92 (23.3)	303 (76.7)	395 (100)	<0.001*
Single	17 (63.0)	10 (37.0)	27 (100)	
Divorced	7 (15.6)	38 (84.4)	45(100)	
Place of residence				
Urban	62 (27.4)	164 (72.6)	226(100)	0.19
Rural	53 (22.3)	185 (77.7)	228 (100)	
Educational status				
Illiterate	4 (14.8)	23 (85.2)	27 (100)	0.006*
Primary school	76 (24.4)	235 (75.6)	311 (100)	
Junior high school	16 (48.5)	17 (51.5)	33 (100)	
High School	8 (15.1)	45 (84.9)	53 (100)	
University	12 (27.9)	31 (72.1)	43 (100)	
Insurance				
Medicare for civil servant	37 (27.6)	97(72.4)	134 (100)	0.40
Medicare for worker	66 (22.7)	225 (77.3)	291 (100)	
Private	3 (42.9)	4 (57.1)	7 (100)	
Other	9 (30.0)	21 (70.0)	30 (100)	
Profession				
Housewife	49 (24.9)	148 (75.1)	197 (100)	0.25
Worker	12 (41.4)	17 (58.6)	29 (100)	
Self-employed	9 (25.7)	26 (74.3)	35 (100)	
Farmer	12 (29.3)	29 (70.7)	41 (100)	
Civil servant	19 (19.0)	81 (81.0)	100 (100)	
Retired	15 (23.4)	49 (76.6)	64 (100)	
Comorbidity				
Yes	51 (32.1)	108 (67.9)	159 (100)	0.004*
No	61 (20.1)	243 (79.9)	304 (100)	
Family history of comorbidity				
Yes	61 (30.5)	139 (69.5)	200 (100)	0.008*
No	52 (19.8)	211 (80.2)	263 (100)	
Family history of cancer				
Yes	45 (30.6)	102 (69.4)	147 (100)	0.03*
No	69 (21.8)	248 (78.2)	317 (100)	
Knowledge about disease				
Yes	96 (23.5)	312 (76.5)	408 (100)	0.42
No	8 (18.2)	36 (81.8)	44 (100)	
Monthly income				
<MW	29 (25.0)	87 (75.0)	116 (100)	0.67
MW up to 2 times MW	64 (23.5)	208 (76.5)	272 (100)	
>2 times MW	11 (33.3)	22 (66.7)	33 (100)	
Social relief	9 (23.7)	29 (76.3)	38 (100)	

MW, minimum wage. *, p significant.

Table 3. Clinical characteristics of patients who used CAM

Characteristics	Yes, n (%)	No, n (%)	Total, n (%)	p
Site of cancer				
Breast cancer	32 (25.2)	95 (74.8)	127 (100)	0.60
Respiratory system	37 (27.8)	96 (72.2)	133 (100)	
Gastrointestinal system	27 (20.5)	105 (79.5)	132 (100)	
Genitourinary system	12 (27.9)	31 (72.1)	43 (100)	
Others	8 (25.0)	24 (75.0)	32 (100)	
Stage of disease				
Metastatic	66 (23.7)	212 (76.3)	278 (100)	0.50
Non-metastatic (early and local advanced)		50 (26.5)	139 (73.5)	189 (100)
Type of therapy (before chemotherapy) : Surgery				
Yes	47 (25.4)	138 (74.6)	185 (100)	0.81
No	69 (24.5)	213 (75.5)	282 (100)	
Type of therapy(before chemotherapy) : Radiotherapy				
Yes	71 (25.4)	209 (74.6)	280 (100)	0.75
No	45 (24.1)	142 (75.9)	187 (100)	
BMI (Body mass index)				
<18.5	3 (15.0)	17 (85.0)	20 (100)	0.32
18.5 – 24.9	45 (24.9)	136 (75.1)	181 (100)	
25.0 – 29.9	48 (28.9)	118 (71.1)	166 (100)	
≥30.0	17 (20.2)	67 (79.8)	84 (100)	

allowed to add further comments. The questionnaire was structured to recover socio-demographic data (age, gender, place of residence, education, income, marital status, profession, family history of chronic disease and cancer, comorbidity, and level of information about disease) and details pertaining to use of CAM among our patients and patient-healthcare staff relations (to share the use of CAM with health professionals). Medical data included diagnosis, stage at diagnosis, current or previous specific anticancer treatment modalities, and body-mass index.

Statistical Analysis

The data were recorded and analyzed using SPSS for Windows, version 17.0 software (SPSS, Inc., Chicago, IL). The X^2 test was used for comparisons between demographic groups. For all statistical analyses, a two-sided p-value of 0.05 was considered sta-

tistically significant. Comparisons were assessed by a X^2 test. Logistic regression analysis was used to analyze potential variables that may have independently influenced the use of CAMs.

RESULTS

The study population consisted of 494 patients, comprised of 258 women (52.2 %) and 236 men (47.8 %). The median age was 58 years, ranging from 24 to 90 years. Socio-demographic characteristics of patients are given in Tables 1 and 2. Table 1 shows patients who had knowledge about CAM therapies, and Table 2 shows the socio-demographic features about CAM use. Table 3 shows the clinical characteristics of patients who used CAM.

Marital status ($p= 0.003$), educational status ($p< 0.001$), monthly income ($p< 0.001$), knowledge about the disease ($p< 0.001$), family history of comorbid-

Table 4. Types of CAM therapies used by cancer patients and features

	n	%
Type of CAM		
Herbal	113	67.3
Vitamins,	25	14.9
Talk to another person (friends, patients, imam, hodja etc.)	18	6.0
Meditation, yoga, acupuncture		
massage prayer	10	10.7
Other (Energy therapies, bioenergy, etc)	2	1.1
Type of plant		
Stinging nettle with without various herbal agents	126	55.5
Pomegranate juice	23	10.1
Raisins	61	26.9
Others	17	7.5
Advised to use		
Family	54	32.9
Friends	56	34.1
Patients	15	9.1
Health professionals	39	23.9
Type of supply		
Shopping	57	54.3
Internet	11	10.5
Other	37	35.2
Do you believe that the method you use will be useful for your treatment?		
Yes	126	61.8
No	78	38.2
Reason for CAM usage		
No benefited from convensional therapy	21	15.8
To add benefit to modern therapy	53	39.8
Advised	48	36.1
Other	11	8.3
To share the use of CAM with doctor		
Yes	81	51.9
No	75	48.1
Cooperation between CAM users and healy professionals		
Yes	81	51.9
No	75	48.1
Has your nurse/medical staff received information about CAM?		
Yes	246	78.6
No	67	21.4

ity ($p < 0.012$), and place of residence (0.004) were statistically significant for knowledge about CAM. But no significant difference was found between who had knowledge about CAM and who had not heard of CAM, with respect to age, gender, insurance, profession, comorbidity, and family history of cancer ($p > 0.05$).

Of the 494 patients, 237 patients (23.5%) had used at least one type of CAM since the time of diagnosis. Marital status ($p < 0.001$), comorbidity ($p = 0.004$), educational status ($p = 0.006$), family history of comorbidity ($p = 0.008$), and family history of cancer ($p = 0.03$) were statistically significant for CAM use. However, age, gender, place of residence, insurance, profession, and comorbidity were not statistically significant ($p > 0.05$). Additionally, type of cancer, stage of disease, type of therapy (radiotherapy, surgery), and BMI (Body mass index) were not statistically significant either.

The most frequently used methods were herbal therapy (67.3%) and vitamins (14.9%) (Table 4). The most commonly used herb was the stinging nettle—alone or in combination (55.5%). The second plant type was raisins (26.9%). CAM agents were generally combined with conventional anti-cancer agents. Agents could easily be obtained from regular herbal stores (or the internet) at a suitable price. Our patients usually prefer to shop from stores (54.3%) versus the internet (10.5%). Interestingly, almost half our patients consulted their physicians about CAM use (51.9%) (Table 4).

Logistic regression analysis showed that educational status ($p = 0.015$), high monthly income ($p = 0.03$), knowledge about the disease ($p = 0.005$), and family history of comorbidity ($p = 0.005$) were statistically significant for knowledge about CAM. Otherwise, only marital status ($p < 0.001$) and comorbidity ($p = 0.04$) were determined as independent factors for CAM use (Tables 5 and 6).

We also found that 78.6% of patients had information about CAM before using it, 34.1% got advice from friends, and 39.8% of patients believed that adding it to modern therapy created a beneficial effect.

DISCUSSION

The increasing interest in CAM among cancer patients may be due to the limitations of conventional cancer therapy.⁶ There is an increased concern about

Table 5. Logistic regression analysis of demographic and clinic determinants of knowledge about CAM **

Characteristics	Odds Ratio	95% CI	P
Educational Status			0.015
Primary school	0.703	0.313-1.580	0.394
Junior high school	1.490	0.472-4.709	0.497
High school	1.138	0.427-3.031	0.797
University	2.597	0.832-8.109	0.100
Illiterate	R		
Monthly income			0.09
<MW	0.717	0.333-1.541	0.394
MW up to 2 times MW	1.351	0.670-2.727	0.401
>2 times MW	3.509	1.115-11.045	0.032
Social relief	R		
Knowledge about disease	3.107	1.410-6.844	0.005
Family history of comorbidity	1.798	1.192-2.710	0.005

**Statistical analyses did not reveal significant differences for the other parameters (including marital status, place of residence)

the use of CAM by oncology patients because potential adverse drug interactions could cause patients to experience increased toxicity or decrease the efficacy of the conventional systemic therapy used to treat cancer.⁷

Ernest and Cassileth summarized 26 studies from 13 countries in adult populations and reported that the frequency of using CAM methods varies from 9% to 64% in patients with cancer. In developed countries, CAM is used by 25% to 50% of the general population.⁸ Our result is within the normal range (23.5%).

In our patients, CAM use was generally limited to

herbal remedies, the most frequent ingredient being the nettle. The use of other known CAM approaches was minimal. The possible explanation for this behavior is being less educated, having a lower income, and a 'traditional society structure'.^{2,3,9} In Turkish culture, the most commonly used herb is reported as nettle leaves/teas and thyme, often mixed with other compounds. Availability is very easy and has a suitable price. Moreover, many people use herbal therapy because of the belief that natural products are safe and the combination with the other therapies is harmless, etc. However, some studies showed that these products do have toxic effects.

TABLE 6. Logistic regression analysis of demographic and clinic determinants of CAM use***

Characteristics	Odds Ratio	95% CI	P
Marital Status			<0.001
Married	1.54	0.66-3.61	0.31
Single	8.06	2.59-25	<0.001
Divorced	R		
Comorbidity	1.6	1.01-2.54	0.04

*** Statistical analyses did not reveal significant differences for the other parameters (including family history of cancer, family history of comorbidity and educational status)

The prevalence of CAM use by ethnicity has been studied. A San Francisco-based study found that African-American women used spiritual healing more frequently than other types of CAM (36%), Chinese women most often reported using herbal remedies (22%), and Latino women used dietary therapies (30%) and spiritual healing (26%).¹⁰

Moreover, Richardson et al. reported a group of mixed cancer patients used CAM because patients hoped to improve their quality of life (77%), boost their immune system (71%), and prolong their life (62%).¹¹ An Italian study showed that patients' main reasons for using CAM were physical distress (61%) and psychological distress (21%).¹² In our study, patients said they used CAM because of "adding benefit to medical therapy" (39.8%), "advised" (36.1%), and "uselessness of conventional therapy" (15.8%). Although there were a high proportion of Turkish patients stating that CAM techniques were not effective in both the studies done by Ceylan et al. and Samur et al. (46.8% and 48.0%, respectively), our study revealed 38.2% of patients stating that CAM was not effective.^{5,13} But Ucan et al. (20.7%) and Tas et al. (7.4%) reported a low percentage of patients stating that CAM techniques were not effective.^{2,3} It may be due to our patients having low educational levels. Only 20% of patients graduated from high school and university. Maybe they did not know how to use the internet.

The socio-demographic factors associated with CAM usage are confirmed by some studies. Patients who are female, younger, and have higher educational levels are more likely to use CAM.^{11,14-16} In our study, multivariate logistic regression analysis showed that only educational status was statistically significant to knowledge about CAM, but we did not correlate the use of CAM ($p=0.015$, $p>0.05$, respectively).

In support of other studies, we found that marital status was associated with CAM usage ($p<0.001$).^{17,18} We also found that comorbidity was statistically significant. Thus, marital status and comorbidity were determined as independent factors for CAM use. It is possible that these patients may be used to other medications and our patients like to take medicine ($p=0.04$).

Cooperation between CAM users and medical staff concerning CAM usage was strong in our study (51.9% of the patients). However, some Turkish studies reported that CAM usage was weak in cooperation^{2,3}.

Many studies showed that patients using CAM learned about this treatment from friends and family.^{2,3,19-21} We also found the same result in our study. However, 23.9% of the patients reported that they learned about CAM from health professionals in the media.

Health professionals need to be able to provide information about CAM to their patients and documentation of CAM use should become part of routine assessment for all cancer patients. Physicians who are willing to communicate openly and in a non-judgmental style about CAM may avoid disrupting the patient-medical staff relationship and possibly encourage compliance with conventional treatment⁶.

Studies show that some herbs, such as feverfew, garlic, ginger, and ginkgo can cause bleeding complications and have been associated with life-threatening perioperative bleeding.²² Some herbs have been associated with liver toxicity that may be particularly dangerous in combination with certain chemotherapies.^{23,24} Few herbs are tested for side effects, quality control, or contamination.

Patient-doctor/medical staff communication and patient education about CAM should be improved. The oncology community must be willing to communicate with patients about CAM, inform them about possible contraindications or benefits, and participate in research to answer questions of safety and efficacy. Patient expectations, psychological reactions, acceptance of health status, and cost and clinical outcomes pertaining to the medical treatment should be evaluated properly. Further large-scale studies are required.

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