International Journal of
HEMATOLOGY

Thalidomide in Chronic Graft-versus-Host Disease after Stem Cell Transplantation: Effects on Quality of Life

Steve Miller,[a] Shalini Sharda,[a] James Rodrigue,[a]
Paulette Mehta[a,b,c]

[a]Departments of Pediatrics and Internal Medicine and the Bone Marrow Transplant Program, University of Florida College of Medicine, Gainesville, Florida; [b]University of Arkansas for Medical Sciences, and the [c]Central Arkansas Veterans Healthcare System, Little Rock, Arkansas, USA

Received February 19, 2002; received in revised form July 11, 2002; accepted July 12, 2002

Abstract

Thalidomide is being increasingly used after stem cell transplantation as immunosuppression for patients with chronic graft-versus-host disease, as well as for antiangiogenesis effects in patients with multiple myeloma, brain tumors, leukemia, or other malignancies. The goal of this study was to determine if thalidomide improved the quality of life by virtue of its associated sleep-promoting, anxiety-reducing, antiwasting, and antidiarrheal effects. We therefore studied 28 patients with resistant chronic graft-versus-host disease who were treated with thalidomide (13 patients) or other immunosuppressive drugs (15) and compared them with healthy control subjects (16). All patients completed quality-of-life questionnaires prospectively before beginning regimens of thalidomide or other immunosuppressive drugs and completed similar questionnaires at 3- and 6-month intervals thereafter. The Transplant Symptom Frequency score was similar for healthy control subjects and both groups of patients with chronic graft-versus-host disease, regardless of whether they had received thalidomide or not. Quality of sleep was equally poor in patients who received or did not receive thalidomide. The most common complaint of patients with chronic graft-versus-host disease was fatigue, followed in frequency by overeating. The control group had similar concerns. This pilot study suggests that patients with chronic graft-versus-host disease have a quality of life similar to that of their health care workers, regardless of whether they are treated with thalidomide or other immunosuppressive drug, and that fatigue and overeating are the most common complaints. *Int J Hematol.* 2002;76:365-369.

Key words: Thalidomide; Quality of life; Graft-versus-host disease; Bone marrow transplantation

1. Introduction

Thalidomide has recently been approved for treatment of chronic graft-versus-host disease after stem cell transplantation (SCT). It is effective in approximately 60% of children and adults with chronic graft-versus-host disease in alleviating their physical symptoms [1-3].

Chronic graft-versus-host disease is one of the most important predisposing factors for poor quality of life after SCT [4]. Many physical aspects of this disease contribute to the poor quality of life and include joint deformities, dry skin, dry eyes, dry mouth, and difficulty in breathing. The disease is associated with a high production of tumor necrosis factor, which induces wasting, poor appetite, fever, and fatigue [5]. Thus, treatment for chronic graft-versus-host disease should address not only physical symptoms of disease but also quality of life.

We speculated that patients with chronic graft-versus-host disease might have an improved quality of life after beginning thalidomide therapy. We reasoned that the sleep-promoting, anxiety-reducing, and antiwasting effects of thalidomide reported for patients with human immunodeficiency virus infection [6,7] could improve the quality of life of bone marrow transplantation patients. To test this hypothesis, we administered self-report questionnaires to patients who presented with chronic graft-versus-host disease between 1999 and 2000 and for whom treatment included or did not include thalidomide.

Correspondence and reprint requests: Paulette Mehta, MD, University of Arkansas for Medical Sciences, 4301 West Markham St, Slot 508, Little Rock, AR 72205, USA (e-mail: MehtaPaulette@uams.edu).

2. Materials and Methods

2.1. Patient Population

Patients were registered in the study if they had clinically evident or biopsy-proven chronic graft-versus-host disease and if they had received and failed to respond to at least 4 days of steroid treatment. All patients or their guardians signed informed consent forms for protocols approved by the University of Florida Institutional Review Board. Patients who were treated with thalidomide signed documents of informed consent for protocol for the use of thalidomide in chronic graft-versus-host disease and for serial quality-of-life evaluations for patients receiving thalidomide. Patients with chronic graft-versus-host disease who were not treated with thalidomide signed informed consent documents for the latter protocol only. Volunteer subjects, mostly hospital employees including doctors and nurses, formed a third group of healthy control subjects who were requested to fill out quality-of-life questionnaires.

In addition, all patients started on thalidomide were registered in the STEPS (System for Thalidomide Education and Prescribing Safety) program and were counseled to avoid pregnancy for themselves or their partners and to store medications safely to prevent their unauthorized use by others. All patients were required to pass a test verifying their understanding of the teratogenic effects of the drug, and they were also required to complete monthly statements to ensure that they were continuing to use proper precautions. Each patient was given a questionnaire to complete before beginning thalidomide treatment and then given 1 per month for 3 months. They were started on 100 mg thalidomide every night at bedtime, and doses were increased to a maximum of 200 mg twice a day as tolerated.

2.2. Control Subjects

Two groups of control subjects were studied. One group consisted of 15 patients with chronic graft-versus-host disease who were not treated with thalidomide. These patients completed questionnaires every month for 3 months in a fashion similar to patients who were treated with thalidomide. The other group consisted of 16 healthy subjects, primarily health care workers who agreed to donate blood and who denied having any underlying disease or intake of medications. These healthy subjects completed the questionnaire 1 time only. A control group of patients undergoing bone marrow transplantation who did not develop chronic graft-versus-host disease was not used, because the primary goal of the study was to determine the impact of thalidomide on patients with established graft-versus-host disease.

2.3. Quality-of-Life Assessment

The quality-of-life assessment was based on the previously described Transplant Symptom Frequency report. Patients were asked to rate on a scale of 0 to 4 how often they experienced different symptoms, in which 0 was never, 1 rarely, 2 sometimes, 3 often, and 4 always. Lower numbers indicated a better quality of life. Patients were asked about mood swings, amount of sleep, varicose veins, depression, bad breath, fatigue, breathing difficulties, changed facial appearance, changed bodily appearance, excessive hair, acne, fragile skin, pain, overeating, poor appetite, diarrhea, nausea, taste sensitivity, swollen ankles, tremors, headaches, weight loss, weight gain, memory problems, anxiety or nervousness, poor concentration, fever, bad vision, frequent palpitations, and sleep difficulties (see Table 1). They were also asked to rate the quality of their sleep from 1 to 5 (1 being poor, 5 being good). All questionnaires were filled out prospectively.

Table 1.
Baseline of Quality-of-Life Scores in Study Subjects

Symptoms	Healthy Controls n = 16	Study Patients n = 13	Control Patients n = 15
Mood swings	1.69	1.77	1.53
Lack of sleep	1.88	1.85	2.07
Varicose veins	0.44	0.38	0.13
Depression	1.19	1.46	1.27
Bad breath	0.94	0.81	1.07
Fatigue	2.00	2.31	2.00
Breathing difficulties	0.44	0.85	0.93
Changed facial appearance	0.31	1.538*	1.8666*
Changed bodily appearance	0.50	1.31	1.933*
Excessive hair	0.19	0.85	0.8†
Acne	0.94	0.54	0.40
Fragile skin	0.44	1.384†	1.6‡
Pain	1.13	1.58	1.73
Overeating	2.53	0.615‡	1.53
Poor appetite	0.25	1.307‡	1.2*
Diarrhea	0.56	0.85	0.80
Nausea	0.50	0.85	1.266*
Taste sensitivity	0.19	1.346‡	1.4*
Swollen ankles	0.06	0.538†	1.4*
Tremors	0.06	0.923†	1.333*
Bruises	0.75	0.38	1.733‡
Headaches	1.44	0.85	1.53
Weight loss	0.38	1.23†	1†
Weight gain	1.38	1.15	1.80
Memory problems	1.38	1.08	1.20
Anxiety or nervousness	1.88	1.69	1.40
Poor concentration	1.19	1.46	1.13
Fever	0.31	0.54	0.47
Poor vision	1.06	1.77	2.2667*
Heart palpitations	0.69	0.31	0.67
Sleep difficulties	1.31	1.69	2.133†
Quality of sleep (1 = poor; 5 = good)	3.81	3.23	2.7‡

*$P < .001$.
†$P < .05$.
‡$P < .005$.

3. Results

3.1. Demographics of Subjects

The study group consisted of patients with chronic graft-versus-host disease who were treated with thalidomide. This group consisted of 13 subjects, 9 male and 4 female patients between the ages of 3 and 59 years (mean, 40 ± 5 years; median, 46 years) with diagnoses of acute lymphoblastic leukemia (2), chronic myelogenous leukemia (6), non-Hodgkin's lymphoma

(1) and chronic lymphoblastic leukemia (1). The first control group consisted of patients with chronic graft-versus-host disease who were not being treated with thalidomide. This group consisted of 15 subjects between the ages of 22 and 65 years (mean, 45 ± 3 years; median, 45 years). Diagnoses were acute lymphoblastic leukemia (1), acute myelogenous leukemia (4), chronic myelogenous leukemia (6), non-Hodgkin's lymphoma (3), and myeloproliferative disorder (1). Of these patients, 7 were women, and 8 were men. The healthy control subjects were individuals between the ages of 25 and 58 years (mean, 38 ± 3 years; median, 38.7 years). Six were men, and 10 were women; all subjects denied any underlying disease or the use of medications.

3.2. Baseline Quality-of-Life Scores of Patients with Graft-versus-Host Disease Compared with Healthy Subjects

Shown in Tables 1-3 are the quality-of-life scores for healthy control subjects and all patients with chronic graft-versus-host disease prior to starting thalidomide or other treatments, after treatment with other therapies, and after treatment with thalidomide. There were no significant differences in the global Transplant Symptom Frequency scores for patients with graft-versus-host disease randomized to thalidomide, patients randomized to other treatments, or healthy controls. Mean scores in these 3 groups were 35.92, 41.79, and 36.44, respectively; *P* was nonsignificant.

3.3. Effects over Time

Repeated tests of analysis of variance for the Transplant Symptom Frequency composite scores did not vary significantly over time for any of the 3 groups. This result includes all times from the baseline through 3 months of follow-up. Results are similarly nonsignificant when analyzed for baseline through the 2-month follow-up or for baseline through the 1-month follow-up.

3.4. Quality of Sleep

Quality of sleep, however, did vary across the 3 groups. Quality of sleep was significantly impaired in patients with

Table 2.
Change in Quality of Life over Time in Patients Not Treated with Thalidomide

Symptoms	Baseline: Control Patients n = 15	1-Month Follow-up: Control Patients n = 13	2-Month Follow-up: Control Patients n = 12	3-Month Follow-up: Control Patients n = 11
Mood swings	1.53	1.54	1.17	1.09
Lack of sleep	2.07	2.08	1.92	2.18
Varicose veins	0.13	0.15	0.08	0.09
Depression	1.27	1.23	1.00	0.73
Bad breath	1.07	0.85	0.42	0.64
Fatigue	2.00	1.77	1.75	1.91
Breathing difficulties	0.93	0.69	1.17	0.91
Changed facial appearance	1.87	1.46	0.92	1.18
Changed bodily appearance	1.93	1.54	0.9166*	1.27
Excessive hair	0.80	0.62	0.75	1.00
Acne	0.40	0.08	0.25	0.18
Fragile skin	1.60	1.77	1.58	1.36
Pain	1.73	1.85	1.67	1.73
Overeating	1.53	0.538*	0.666*	0.545†
Poor appetite	1.20	1.00	0.75	0.73
Diarrhea	0.80	0.62	0.25*	0.45
Nausea	1.27	1.38	1.08	1.09
Taste sensitivity	1.40	1.62	1.50	0.82
Swollen ankles	1.40	1.08	1.00	1.09
Tremors	1.33	1.00	0.83	0.82
Bruises	1.73	1.31	1.17	1.27
Headaches	1.53	1.15	1.33	1.45
Weight loss	1.00	0.69	0.75	0.55
Weight gain	1.80	0.692†	0.8333*	1.27
Memory problems	1.20	1.08	0.92	0.82
Anxiety or nervousness	1.40	1.54	1.50	1.36
Poor concentration	1.13	1.00	0.67	0.82
Fever	0.47	0.23	0.33	0.55
Poor vision	2.27	2.62	2.00	2.18
Heart palpitations	0.67	0.31	0.50	0.55
Sleep difficulties	2.13	2.00	2.42	2.55
Quality of sleep (1 = poor; 5 = good)	2.70	2.77	2.92	2.64

*$P < .05$.
†$P < .005$.

Table 3.
Change in Quality of Life over Time in Patients Treated with Thalidomide

Symptoms	Baseline: Thalidomide Patients n = 13	1-Month Follow-up: Thalidomide Patients n = 11	2-Month Follow-up: Thalidomide Patients n = 10	3-Month Follow-up: Thalidomide Patients n = 8
Mood swings	1.77	1.86	1.90	1.63
Lack of sleep	1.85	1.00	1.70	0.875*
Varicose veins	0.38	0.09	0.00	0.00
Depression	1.46	1.36	1.40	1.38
Bad breath	0.81	0.64	0.70	0.38
Fatigue	2.31	2.73	2.70	2.81
Breathing difficulties	0.85	0.82	1.10	1.50
Changed facial appearance	1.54	1.45	1.70	1.75
Changed bodily appearance	1.31	1.00	1.20	1.50
Excessive hair	0.85	0.64	0.60	0.125*
Acne	0.54	0.55	0.50	0.00
Fragile skin	1.38	1.18	1.90	1.25
Pain	1.58	1.73	2.00	2.00
Overeating	0.62	0.73	0.20	0.13
Poor appetite	1.31	0.91	1.20	0.63
Diarrhea	0.85	0.91	1.00	0.88
Nausea	0.85	0.82	1.20	0.88
Taste sensitivity	1.35	1.27	0.80	1.25
Swollen ankles	0.54	0.91	0.90	0.88
Tremors	0.92	1.18	1.00	1.25
Bruises	0.38	0.73	0.30	0.88
Headaches	0.85	1.00	1.10	1.13
Weight loss	1.23	0.73	0.70	1.13
Weight gain	1.15	1.36	1.20	1.13
Memory problems	1.08	1.09	1.10	1.13
Anxiety or nervousness	1.69	1.27	1.40	1.38
Poor concentration	1.46	1.36	1.10	1.63
Fever	0.54	0.09*	0.20	0.125*
Poor vision	1.77	1.82	1.90	2.38
Heart palpitations	0.31	0.09	0.40	0.00
Sleep difficulties	1.69	0.82*	1.55	0.625*
Quality of sleep (1 = poor; 5 = good)	3.23	3.55	3.65	4*

*$P < .05$.

graft-versus-host disease (whether or not they were randomized to the thalidomide or to the no-thalidomide arm of the study) compared with healthy control subjects.

4. Discussion

Quality of life after bone marrow transplantation has been the subject of many studies, and the results have been conflicting [8-17]. Most of the reported studies suggest that after bone marrow transplantation patients have an essentially normal quality of life compared with age-matched controls. Other studies have suggested that patients may suffer from low self-esteem, psychological distress, occupational disability, impaired social, marital, and family relationships, and persistent sleep difficulties. There are also studies showing that patients who undergo bone marrow transplantation have an enhanced quality of life, compared with age-matched controls, owing to a perception of a new meaning in life, redirected life priorities, increased compassion, improved social, marital, and family relationships, and heightened spirituality. No study has shown that any particular immunosuppressive medication for the autoimmune complications of bone marrow transplantation (such as chronic graft-versus-host disease) has an impact on quality-of-life measurements.

The results of this small pilot study show that patients with chronic graft-versus-host disease have a global Transplant Symptom Frequency score similar to those of healthy control subjects. This finding suggests that many patients have a normal quality of life after bone marrow transplantation despite chronic graft-versus-host disease. Other investigators similarly have found that quality of life after bone marrow transplantation is often satisfactory and that chronic graft-versus-host disease is not an important factor in impairing quality of life after transplantation. For example, Andrykowski et al evaluated quality-of-life outcomes with a questionnaire completed by 200 adult bone marrow transplant recipients from 5 bone marrow transplant centers. Factors found to be *unassociated* with quality of life after bone marrow transplantation related to disease diagnosis, dose of total body irradiation, presence or absence of chronic graft-versus-host disease, type of graft-versus-host-disease prophylaxis, and extent of marrow graft match. Risk factors that did correlate to poorer quality of life after transplantation related to non–graft-versus-host disease factors, such as greater age at time of transplantation, lower level of educa-

tion, and more advanced disease at the time of bone marrow transplantation [15,16].

The only significant difference between the patients with chronic graft-versus-host disease and healthy control subjects in this study was quality of sleep. Patients with chronic graft-versus-host disease had impaired sleep whether or not they were randomized to receive thalidomide. Sleep difficulties have been well described as persistent problems for patients with cancer and for patients who have undergone bone marrow transplantation [17]. This difference between patients with chronic graft-versus-host disease and healthy subjects persisted at each of the periods evaluated. The reasons for impaired sleep were not investigated but may have related to pain, medications (eg, prednisone), anxiety, fear, or other factors.

The most common complaint of patients with chronic graft-versus-host disease was fatigue. This complaint was also a common complaint in the healthy control group and was second only to overeating. The control group consisted of health care workers, mostly doctors and nurses treating the patients with disease, and their fatigue may be related to their own sleep deprivation because of their irregular schedules, their own anxieties and stresses, or their association with fatigued patients.

There are several limitations to our study. First, the study population is small. Second, the control subjects with whom the patients with chronic graft-versus-host disease were compared were healthy. A better control group might have been subjects who had undergone stem cell transplantation but who had not developed chronic graft-versus-host disease. However, the primary goal of this study was to measure the impact of thalidomide for patients with chronic graft-versus-host disease, and therefore only patients with chronic graft-versus-host disease were studied.

Thalidomide is increasingly being used for patients with cancer, including patients with multiple myeloma, plasma cell leukemia, Kaposi sarcoma, renal cell carcinoma, advanced breast cancer and colon cancer, prostate cancer, glioma, and myelodysplastic syndrome [18,19]. It is also being increasingly used for nonmalignant conditions such as Crohn disease, rheumatoid arthritis, ankylosing spondylarthritis, systemic sclerosis, and others [20]. Because many of these diseases are incurable, quality of life becomes an essential criterion by which to evaluate and prioritize medications.

References

1. Mehta P, Kedar A, Graham Pole J, Skoda-Smith S, Wingard JR. Thalidomide in children undergoing bone marrow transplantation: series at a single institution and review of the literature. *Pediatrics*. 1999;103:44-49.
2. Cole CH, Rogers PC, Pritchard S, Phillips G, Chan KW. Thalidomide in the management of chronic graft-versus-host disease in children following bone marrow transplantation. *Bone Marrow Transplant*. 1994;14:937-942.
3. Vogelsang GB, Farmer ER, Hess AD, et al. Thalidomide for the treatment of chronic graft-versus-host disease. *N Engl J Med*. 1992; 326:1055-1058.
4. Baker F, Wingard JR, Curbow B, et al. Quality of life of bone marrow transplant long term survivors. *Bone Marrow Transplant*. 1994; 13:589-596.
5. Yeh SS, Schuster MW. Geriatric cachexia: the role of cytokines. *Am J Clin Nutr*. 1999;70:183-197.
6. Jacobson JM, Greenspan JS, Spritzler J, et al. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. *N Engl J Med*. 1997;336:1487-1493.
7. Jacobson JM, Spritzler J, Fox L, et al. Thalidomide for the treatment of esophageal aphthous ulcers in patients with human immunodeficiency virus infection. National Institute of Allergy and Infectious Disease AIDS Clinical Trials Group. *J Infect Dis*. 1999; 180:61-67.
8. Kiss TL, Abdolell M, Jamal N, Minden MD, Lipton JH, Messner HA. Long term medical outcomes and quality of life assessment of patients with chronic myeloid leukemia followed at least 10 years after allogeneic bone marrow transplantation. *J Clin Oncol*. 2002; 20:2334-2343.
9. Heinonen H, Volin L, Uutela A, Zevon M, Barrick C, Ruutu T. Quality of life and factors related to perceived satisfaction with quality of life after allogeneic bone marrow transplantation. *Ann Hematol*. 2001;80:137-143.
10. Saleh US, Brockopp DY. Quality of life one year following bone marrow transplantation: psychometric evaluation of the quality of life in bone marrow transplant survivors tool. *Oncol Nurs Forum*. 2001;28:1457-1464.
11. Curbow B, Somerfield MR, Baker F, Wingard JR, Legrow MW. Personal changes, dispositional optimism, and psychological adjustment to bone marrow transplantation. *J Behav Med*. 1993;16: 423-443.
12. Ferrell B, Grant M, Schmidt GM, et al. The meaning of quality of life for bone marrow transplant survivors. Part 2. Improving quality of life for bone marrow transplant survivors. *Cancer Nurs*. 1992; 15:247-253.
13. Fromm K, Andrykowski MA, Hunt J. Positive and negative sequelae of bone marrow transplantation: implications for quality of life assessment. *J Behav Med*. 1996;19:221-250.
14. Andrykowski MA, Bady MJ, Hunt JW. Positive psychosocial adjustment in potential bone marrow transplant recipients: cancer as a psychosocial transition. *Psychooncology*. 1993;2:261-276.
15. Andrykowski MA, Greimer CB, Altmaier EM, et al. Quality of life following bone marrow transplantation: findings from a muticentre study. *Br J Cancer*. 1995;71:1322-1329.
16. Andrykowski MA, Henslee PJ, Farrall MG. Physical and pyschosocial functioning of adult survivors of allogeneic bone marrow transplantation. *Bone Marrow Tranplant*. 1989;4:75-81.
17. Savard J, Morin CM. Insomnia in the context of cancer: a neglected problem. *J Clin Oncol*. 2001;19:895-908.
18. Singhal S, Mehta J. Thalidomide in cancer. *Biomed Pharmacother*. 2002;56:4-12.
19. Richardson P, Hideshima T, Anderson K. Thalidomide: emerging role in cancer medicine. *Annu Rev Med*. 2002;53:629-657.
20. Combe B. Thalidomide: new indications? *Joint Bone Spine*. 2001; 68:582-587.