Thalidomide in Children Undergoing Bone Marrow Transplantation: Series at a Single Institution and Review of the Literature

ABSTRACT. Thalidomide has one of the most notorious drug histories because of its teratogenicity. Its widespread use in the 1960s led to a worldwide epidemic of phocomelia in inborns; this in turn led to its complete ban in most of the world. However, it has now been licensed for selected indications including graft-versus-host-disease (GVHD) after bone marrow transplantation, wasting associated with tuberculosis and human immunodeficiency virus infection, and leprosy. Little is known, however, about its use in children in these settings. Therefore, we report our experience and review the literature on thalidomide in children for GVHD after bone marrow transplantation. We studied 6 patients, 2 with chronic GVHD, 2 with acute GVHD, and 2 with acute GVHD progressing into chronic disease. One patient with chronic GVHD had a complete response, whereas the other had a partial response. Side effects consisted primarily of sedation and constipation, which are reported previously and well known side effects. None had neuropathy. One patient had rash, eosinophilia, and early pancreatitis that began shortly after initiation of thalidomide, persisted, and resolved only after discontinuation of thalidomide. Eosinophilia and pancreatitis are both previously unreported side effects or associated findings of thalidomide treatment. Review of the literature reveals three major studies of thalidomide in GVHD; of these two included children and adults together, and one in which age range of patients was not mentioned. In addition, four series of children receiving only thalidomide are reported. These series contained 1 to 14 patients each.

Results show efficacy in at least 50% of children with chronic GVHD and little or no efficacy in children with exclusively acute GVHD. Side effects are similar to those reported in adults and consisted mostly of sedation and constipation, both of which subsided over time and resolved after discontinuing the drug. We speculate on the reasons for which thalidomide is more effective in chronic, compared with acute, GVHD in children, and make recommendations for future study. Pediatrics 1999; 103(4). URL: http://www.pediatrics.org/cgi/content/full/103/4/e44; thalidomide, BMT, GVHD.

ABBREVIATIONS. GVHD, graft-versus-host disease; ATG, antithymocyte globulin; SCIDS, severe combined immunodeficiency syndrome; WBC, white blood cell; HLA, human leukocyte antigen.

Thalidomide has one of the most notorious drug histories in the United States. Its use in pregnant women leading to an epidemic of phocomelia among newborns remains a shocking chapter in medicine. Thus, the recent decision to lift the ban on thalidomide and to approve its use for selected indications has attracted great attention.1-4 Because thalidomide now has been licensed, it is necessary that all pediatricians become familiar with its indications, contraindications, and safety profile, apart from its teratogenicity.

Little is known about thalidomide in children, precisely because it has been banned in the United States. Despite the ban, however, the drug has been used intermittently over the past 2 decades and has found a place as an inhibitor of tumor necrosis factor. The Food and Drug Administration estimates that there are at least 1000 patients in this country presently receiving thalidomide on a compassionate basis or in clinical trials.2 Most of the clinical indications for thalidomide are wasting associated with human immunodeficiency virus and tuberculosis, Behcets disease, leprosy, and chronic graft-versus-host disease (GVHD). However, little data are available on these or other patients, especially children.

Although distribution of the drug will be strictly controlled, it will be used in selected children, particularly those with GVHD after bone marrow transplantation, those with cachexia from human immunodeficiency virus or tuberculosis, or those with leprosy.

We therefore review here our experience with thalidomide in children suffering from acute or chronic GVHD after bone marrow transplantation and review case reports and series in which children, alone or with adults, have been studied.

MATERIALS AND METHODS

Experience at the University of Florida

We studied thalidomide use in children undergoing bone marrow transplantation who developed GVHD. All patients were treated according to an institutional protocol. The protocol was approved by the University of Florida Institutional Review Board. All patients were treated first with front-line conventional anti-GVHD therapy including steroids, tacrolimus, cyclosporine, and/or antithymocyte globulin (ATG). If they had no response after 2 weeks, they were started on thalidomide in doses of 12.5 to 25 mg/k per day; this was increased gradually as tolerated. Guidelines were written in a protocol approved by the University of Florida Institutional Review Board. A parent or legal guardian was required to sign informed consent before any therapy with thalidomide was started. Thalidomide was obtained from the manufacturer (Celgene Corp, Warren, NJ). Demographics of the patients are shown Table 1. Briefly, 6 children were studied; of these 2 had chronic GVHD, 2 had acute GVHD progressing into chronic GVHD, and 2 had early acute GVHD. Children were between 1.5 and 17 years of age; all were males. Underlying diseases were severe combined immunodeficiency syndrome (SCIDS),1 acute myelogenous leukemia,2 chronic myelogenous leukemia,2 and non-Hodgkin’s lymphoma secondary to acute lymphoblastic leukemia.

Patients had GVHD involving skin (all 6), gastrointestinal tract,3 liver,2 and joints.2 All had been treated with steroids, 1 had

http://www.pediatrics.org/cgi/content/full/103/4/e44
received ATG, and all had received prophylaxis with cyclosporine and methotrexate as part of their prophylactic regimen for GVHD.

**Literature Review**

A review of all worldwide cases of thalidomide in children with GVHD after bone marrow transplantation was conducted using MEDLINE search. The search extended from 1960 to the present.

**RESULTS**

**Experience at the University of Florida**

**Effects in Chronic GVHD**

One patient with chronic GVHD had a complete response to thalidomide and was able to taper off of his other medications. He received thalidomide for a total of 6 months. At this time, his GVHD has been in complete remission for >2 years. The other patient has been receiving thalidomide for 3 months and has been able to taper off prednisone without flare of his GVHD.

**Effects in Progressive Acute GVHD**

In 2 patients, acute GVHD began within 30 days of bone marrow transplantation and progressed into chronic GVHD, defined as GVHD after 100 days from transplant. Neither had a partial or complete response. One of these children developed excessive somnolence, sleeping 18 of 24 hours each day; thalidomide was discontinued at the parents’ insistence. This child had had radiation-induced somnolence syndrome in the past and may have been predisposed to excessive somnolence. The other child receiving thalidomide had progressive skin grade IV GVHD and was switched to Atgam therapy within 2 weeks because of progressive skin disease.

**Effects in Early Acute GVHD**

Neither of the patients with early acute GVHD had complete resolution of disease. One had partial response in that thalidomide allowed for prednisone tapering, the other died before thalidomide could be evaluated fully. The first patient, a 1.5-year-old infant with SCIDS secondary to ZAP-70 deficiency experienced a rash, eosinophilia, and early pancreatitis. The findings were attributed initially to cotrimoxazole, but symptoms continued even after its discontinuation. Subsequently, the fever, rash, and eosinophilia resolved after discontinuation of thalidomide. This side effect has not been reported previously. Thalidomide allowed this infant to taper to lower doses of steroids than previously. The other child with early acute GVHD died within 2 weeks of being started on thalidomide. He died from adenoviral pneumonia and had no evidence of toxicity to thalidomide.

Thus, one complete and one partial response was seen in the 2 children with chronic GVHD. A partial response in terms of allowing for a steroid-sparing effect was seen in 1 of 2 children with early acute GVHD; the other 3 children with early acute GVHD had no response to thalidomide. In 2 of these 3 cases, however, the medication was discontinued too early to be evaluated fully. Thalidomide was stopped early.

| TABLE 1. Children Receiving Thalidomide for GVHD at the University of Florida |
|-----------------------------|------------------|-------------------|--------------------------|
| Patient Age (y) | Underlying Disease | Type GVHD | Acute Overall Grade | Chronic | Response After 1 Month | Response After 3 Months | Toxicity Overall |
| 1 | 1.5 SCIDS | Skin, GI (II) | | | Partial response | Prednisone tapered | Stopped secondary to eosinophilia, patient was able to taper off prednisone |
| 2 | 5 Acute myelogenous leukemia | GI, skin, liver (III) | Progressive from acute GVHD | | Partial response | Prednisone tapered | Stopped secondary to somnolence |
| 3 | 6 Non-Hodgkin’s lymphoma | Skin (IV) | | | None | Prednisone tapered | Prednisone discontinued |
| 4 | 17 Acute myelogenous leukemia | GI, skin, liver (IV) | Progressive from acute GVHD | | None | None | Prednisone tapered |
| 5 | 5 Chronic myelogenous leukemia | GI, skin, liver (IV) | None | | None | Prednisone tapered | Prednisone tapered |
| 6 | 17 Chronic myelogenous leukemia | Muscle, skin, joints (extensive) | | | Partial response | None | None |

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because of death, toxicity, or progressive disease requiring alternate therapy.

Side Effects

Side effects were tolerable in 4 patients but required discontinuation of the drug in 2 patients. Somnolence and constipation were the side effects noted most frequently. In 1 patient, somnolence was significant enough to discontinue thalidomide. Patients usually develop tolerance to this side effect, but the parents were unwilling to wait for tolerance because of their previous experience with the child’s episodes of somnolence after radiation therapy.

One child suffered from a previously unidentified syndrome of rash, eosinophilia, and pancreatitis. The symptoms began shortly after starting thalidomide. Eosinophil counts reached 6760/mm$^3$ (white blood cell [WBC] count, 13 000/mm$^3$ with 52% eosinophils) within days of beginning thalidomide. Discontinuance of other medications (ie, cotrimoxazole) did not alter this syndrome. Discontinuation of thalidomide, however, resulted in prompt resolution of the fever, rash, eosinophilia, and pancreatitis.

Case Reports of Complete and Partial Responders

NL is a 6-year-old white boy who underwent bone marrow transplantation in March 1996. He had presented with chronic myelogenous leukemia in August 1995, when he was shown to have leukocytosis (WBC count, 158 000/mm$^3$) with numerous blasts and immature cells. Philadelphia chromosome was present in bone marrow cells. He was started on interferon and hydroxyurea and underwent bone marrow transplantation in March 1996 using cyclophosphamide and total body irradiation as the conditioning regimen. He then was reinfused with stem cells obtained from the bone marrow of his human leukocyte antigen (HLA)-identical brother. He had no evidence of GVHD, but 9 months after transplant, was noticed to be in molecular relapse with 2 of 20 chromosomes positive for the Philadelphia chromosome. Therefore, he underwent adoptive immunotherapy using HLA-matched brothers’ (donor) peripheral blood CD$^+$ cells. He received 1 $\times$ 10$^7$ cells/kg in January, March, and again in May 1997. Two months after the last dose of immunotherapy, he was in clinical and molecular remission of chronic myelogenous leukemia and has stayed in remission. Since that time, however, he developed chronic GVHD manifesting as eosinophilic fasciitis with contractures of upper and lower legs and with eosinophilia in peripheral blood and in muscle tissue. Muscle biopsy in November 1997 confirmed the diagnosis. He was treated with high-dose steroids and tacrolimus for chronic GVHD and began aggressive physical therapy. Prednisone was tapered several times, but each time the GVHD flared. Therefore, he was started on thalidomide in August 1998. Since that time, prednisone has been tapered completely without any flares of GVHD, although the patient continues on tacrolimus and thalidomide therapy. The contractures are improving gradually with vigorous physical therapy and continued immunosuppressive therapy.

BJ underwent bone marrow transplantation in February 1998 for SCIDS attributable to ZAP-70 deficiency. The patient received busulfan, cyclophosphamide, and Atgam as conditioning and was then reinfused with T cell-depleted stem cells obtained from the bone marrow of his haploidentical mother. He received cyclosporine and methotrexate for standard prophylaxis against GVHD. He did well after transplantation except for occasional fever, rash in hands and feet, and edema of extremities. Diagnosis of acute GVHD was established by skin biopsies, and the patient was started on prednisone in addition to cyclosporine. Prednisone taper was attempted several times, but resulted in flares of the acute GVHD each time. He was therefore started on thalidomide in April 1998 for continuing and resistant GVHD involving the skin and the gastrointestinal tract. Over the next 2 weeks, the patient was tapered to low doses of steroids. However, eosinophilia occurred (WBC count peaked at 13 000/mm$^3$, with 52% eosinophils). Septra was discontinued and eosinophil counts remained high. The patient also developed pancreatitis and this, in combination with the eosinophilia, required cessation of thalidomide. The eosinophilia resolved completely when thalidomide was discontinued. The patient was not rechallenged with thalidomide.

SG was diagnosed as having chronic myelogenous leukemia in early 1994. He was treated with interferon and conventional chemotherapy until October 1994, when he was referred to Shands Hospital (Gainesville, FL) for bone marrow transplantation. He received conditioning with cyclophosphamide, cytosine arabinoside, and total body and splenic radiation, and he then was reinfused with stem cells from his HLA-identical brother. He developed pancytopenia, fever, mucositis, and seizures secondary to cyclosporine in the period immediately after bone marrow transplant. He also developed acute GVHD that involved skin only (~40% skin surface), and he was treated with and responded to prednisone (4 mg/kg per day). His GVHD was relatively stable, but flared during each attempt to taper prednisone. In August 1995, he was readmitted to Shands Hospital for grade 1 to 2 chronic GVHD of his skin; he was restarted on high-dose prednisone and cyclosporine and again responded well. However, acute GVHD progressed with left elbow contractures, for which he required extension braces, physical therapy, and orthopedic consultations. He developed chronic sclerodermatoid changes and myositis of his upper arm, and forearm muscles intermittently required bolus doses of prednisone along with cyclosporine. In December 1995, he developed herpes zoster and the chronic GVHD was exacerbated. In early 1996, he was begun on Imuran with the intent to taper prednisone; cyclosporine was continued at the same dose. Despite triple therapy with Imuran, steroids, and cyclosporine, however, his chronic GVHD progressed, with swelling of the left arm and increasingly limited extension of forearms. The patient also developed progressive weakness, fatigue, poor appetite, and weight loss. Finally, in October 1996, he was started on thalidomide, 200 mg QID. Within 2
months, by December 1996, the skin rash had resolved, and the joint stiffness and intermittent fevers were much improved. He experienced sleepiness from the thalidomide and some tingling of his arms and legs; both of these problems abated over the subsequent 2 weeks. By January 1997, all signs of chronic GVHD had disappeared; his mouth was moist, he had no lichenoid changes, skin was soft and pliable, and range of motion of all his extremities had returned to normal. In February 1997, he again developed a skin rash and was restarted on thalidomide for 2 weeks. After discontinuation of thalidomide this time, the rash did not return. By December 1997, all the other immunosuppressive medications also had been discontinued, and the patient was off all medications, attending college and working, and feeling well.

**EFFECTS OF THALIDOMIDE IN CHILDREN WITH GVHD IN OTHER STUDIES**

Table 2 lists the other studies in which thalidomide has been used in patients with acute GVHD. In two series,5,6 children were included in a predominantly adult study population, and data were not analyzed separately. In another study using thalidomide for prophylaxis against GVHD,7 age range of patients was not specified. In this study, a paradoxical increase in chronic GVHD, and decrease in survival, was noted.

In four other reports,8–12 children with chronic GVHD were studied exclusively. These series each had small numbers of patients (6 to 14 children). Toxicity was seen in a high proportion of these cases, although usually it did not result in discontinuation of the drug. Toxicity was mild and consisted primarily of sedation in most patients and constipation present in >50% of patients. Rash, neutropenia, and neuritis were other side effects. Neutropenia was cited in a single study only6 and stresses the need for close monitoring.

**DISCUSSION**

These studies suggest that thalidomide may be used safely in children. The safety profile in our patients is similar to that described by others and is less toxic than that of most other antiinflammatory drugs used to treat GVHD such as ATG, cyclosporine, or others. However, information is very preliminary and high vigilance will be necessary for unexpected toxicity.

In most series, thalidomide has been used for chronic GVHD. In these settings, it often is effective to reduce the amount of steroids or other immunosuppressive therapy treatments used concomitantly. It also has been shown to be effective in causing complete and or partial remissions, even in high-risk or refractory chronic GVHD.

In contrast, thalidomide has been used only rarely in acute GVHD. Early laboratory studies suggested that the drug may be effective in acute GVHD, at least in rats.13 Such results, however, have not been replicated in humans. None of our patients had a complete response to thalidomide after having failed alternate treatment. Our experience agrees with that of other groups in which patients with acute GVHD did not respond to thalidomide.

There are several reasons for which thalidomide may be more effective in chronic than in acute GVHD. First, thalidomide is available only as an orally administered drug. During acute GVHD, the gastrointestinal tract is usually injured with mucosal damage and crypt loss. Consequently, thalidomide may not be absorbed adequately through the damaged wall. Second, plasma levels of thalidomide are not easily obtainable, and drug levels may not be adequate. It is possible that many patients with acute GVHD may have failed to respond because of subtherapeutic levels. Third, thalidomide is slow-acting and requires more time than that usually affordable in the treatment of acute GVHD. Thus, when reserved as a last-resort agent treatment for refractory

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**TABLE 2.** Review of Literature of Children Receiving Thalidomide

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Children</th>
<th>Type of Disease</th>
<th>Response</th>
<th>Toxicity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vogelsang et al</td>
<td>Not stated (44 patients, 3–50 y)</td>
<td>Chronic GVHD</td>
<td>Complete response, 14; partial response, 12; no response, 18</td>
<td>Sedation (all), constipation, neuritis</td>
<td>5</td>
</tr>
<tr>
<td>Parker et al</td>
<td>Not stated (80 patients, 6–50 y)</td>
<td>Chronic GVHD</td>
<td>Complete response, 9; partial response, 12 stopped secondary to toxicity, 29</td>
<td>Significant side effects in 29 included sedation, constipation, neuritis, rash, neutropenia (all reversible except neuritis)</td>
<td>6</td>
</tr>
<tr>
<td>Chao et al</td>
<td>28 patients (age not stated)</td>
<td>Prophylaxis for chronic GVHD</td>
<td>Paradoxical detrimental effect</td>
<td>Constipation, sedation</td>
<td>7</td>
</tr>
<tr>
<td>Cole et al</td>
<td>5 (6 mo–12 y)</td>
<td>Chronic GVHD</td>
<td>Spared other immunosuppressive drugs in all patients</td>
<td>Mild somnolence in 1 only</td>
<td>8</td>
</tr>
<tr>
<td>McCarthy</td>
<td>3 (11, 15, 19 y)</td>
<td>Chronic GVHD</td>
<td>Complete response, 2; partial response, 1</td>
<td>Mild</td>
<td>9</td>
</tr>
<tr>
<td>Heney D et al</td>
<td>2 (2, 4 y)</td>
<td>Chronic GVHD</td>
<td>Complete response, 1; no response, 1</td>
<td>Somnolence</td>
<td>10</td>
</tr>
<tr>
<td>Ringden et al</td>
<td>1 (13 y)</td>
<td>Acute GVHD</td>
<td>Progressive disease</td>
<td>None</td>
<td>11</td>
</tr>
<tr>
<td>Rovelli et al</td>
<td>14 children (1–18 y)</td>
<td>Chronic GVHD</td>
<td>Complete response, 6; partial response, 4; progressive disease, 4</td>
<td>Minimal</td>
<td>12</td>
</tr>
</tbody>
</table>
disease, thalidomide may be used too late. It is possible that the early judicious use of thalidomide, perhaps in combination with steroids, at the first sign of GVHD may be more beneficial.

In our series, thalidomide was reasonably safe, especially compared with other immunosuppressive agents used to treat GVHD. Somnolence and constipation were common side effects; neuropathy was not seen in any of our patients. One patient had previously unreported findings of fever, rash, eosinophilia, and pancreatitis. All side effects, however, subsided after discontinuation of thalidomide.

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REFERENCES
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