
Clinical and Laboratory Observations

Pentostatin for the Treatment of Chronic Graft-Versus-Host Disease in Children

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Summary: Chronic graft-versus-host disease (cGVHD) is a major barrier to successful allogeneic stem cell transplantation. Pentostatin has been used to treat cGVHD in a small series of pediatric patients. The authors report the results of the first five pediatric patients receiving pentostatin for refractory cGVHD at Johns Hopkins Hospital. In this early experience, the authors saw considerable symptom response in their patients. Every patient in this series demonstrated a significant improvement in skin and oral symptoms. An increased incidence of infection secondary to pentostatin was not observed. No patient was permanently discontinued from pentostatin subsequent to side effects. If these promising results continue, a trial of pentostatin as a first-line therapy for cGVHD should be considered to potentially reduce our dependence on high-dose steroids for its treatment.

Key Words: bone marrow transplant, graft-versus-host disease, pentostatin

Graft-versus-host disease is the major barrier to successful allogeneic stem cell transplantation. Historically, it has been classified as either acute or chronic. Chronic graft-versus-host disease (cGVHD) develops in 35% to 50% of all patients after transplant¹ and is a significant cause of morbidity and mortality. While the incidence of cGVHD in children has been reported to be lower than the incidence in the adult population,² the morbidity is even more significant in children as the effects may remain with the child lifelong.

Multiple theories exist regarding the pathophysiology of cGVHD. Some believe it is an alloreactive process and a continuation of acute GVHD; others favor an autoreactive process resulting from thymic dysregulation.³ The latter view is supported by animal models that have suggested that this is a Th2-mediated disease, which has also been impli-

cated in autoimmune disorders. Chronic GVHD is an immunologically mediated disease in either model.

Pentostatin (Nipent, SuperGen Inc., Dublin, CA, U.S.A.) is a purine nucleoside analog that inhibits adenosine deaminase, an enzyme expressed in lymphocytes that mediates the recycling of purines. Deficiency of this enzyme leads to a build-up of deoxyadenosine-5'-triphosphate (dATP), which eventually results in apoptosis of B cells and T cells.^{4,5} Therefore, acting as an immunosuppressant, pentostatin should offer a new treatment for cGVHD. Pentostatin is currently approved for the treatment of hairy cell leukemia in adults⁶ and is being investigated for a number of other disorders, including acute/chronic GVHD, GVHD prophylaxis in bone marrow transplant preparative regimens, chronic lymphocytic leukemia (CLL), low-grade lymphoma, and psoriasis.

Significant toxicities such as neurologic, renal, and pulmonary complications were noted during phase I trials in patients with lymphocytic malignancies.⁵ However, in these trials, the most prevalent side effects seen were infection, nausea, vomiting, and fatigue. Most patients were treated with 4 mg/m² per dose biweekly. At this dosage, adenosine deaminase activity is inhibited in lymphocytes, but life-threatening toxicity is seen only in patients with underlying renal insufficiency.⁷ Early data about the treatment of cGVHD with pentostatin in adults reveal a rate of at least a partial response without any progression of disease of 60%.⁸ There is little information on responses to treatment in children with cGVHD. It is important to examine response rates of children to pentostatin independent of the response rates of adults because we are still unsure how cGVHD in children compares with the disease in adults, whose immune system has further evolved. This report describes five children with cGVHD who were treated at Johns Hopkins Hospital with pentostatin.

METHODS

The treatment plan for these five patients is based on our protocol evaluating pentostatin as treatment of refractory

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cGVHD. Three of our five patients were enrolled in this study. One patient was not enrolled in the study because he was treated before the study was planned. The only significant deviation from the protocol was that the patient was treated with a different dosing schedule for the first 6 weeks of therapy (every-week dosing at half the dose). Another patient was not enrolled because she lives in another country and could not return for follow-up appointments. Eligible patients had active or progressive cGVHD that had been refractory to standard therapy. Refractory disease was defined as failure of one or more immune suppressive therapies, including at least 1 mg/kg of steroids given every other day for 3 months. Patients received pentostatin 4 mg/m² every other week for 24 weeks. Patients with creatinine clearance less than 50 mL/min per 1.73 m² were to be given a reduced dose. The primary endpoint was response to therapy, defined as improvement of symptoms. All patients were also observed for toxicity. Response was evaluated every month by the primary oncologist and every 3 months at Johns Hopkins Hospital. At each visit to Johns Hopkins an extensive evaluation was performed, including percentage and extent of skin and fascia involvement, range of motion measurements, liver function tests, and oral examination. Patients continuing to respond at the conclusion of the 24-week course were allowed to continue on the medication off-study.

Patients on study receive Bactrim and penicillin VK until 6 months following resolution of active GVHD for infection prophylaxis. Valtrex or acyclovir was given until 6 months following the final pentostatin dose.

CASE REPORTS

Patient 1

A 22-month-old girl received a matched allogeneic peripheral blood stem cell transplant for beta thalassemia major. Her preparative regimen included busulfan and cyclophosphamide. Her GVHD prophylaxis was initially methotrexate and cyclosporin, but 3 months after transplant she was switched to methotrexate and prednisone secondary to anemia. She did not have acute GVHD but 6 months after transplant developed chronic skin GVHD that progressed through prednisone and tacrolimus (FK506) therapy.

One year after the onset of cGVHD, mycophenolate mofetil was added to the FK506 for the progression of sclerodermatous changes in multiple areas of her upper body. Four months later, her symptoms had severely worsened. Her skin changes progressed down her legs and patchy areas of alopecia were noted. Her eyelids appeared retracted and inverted and completely obscured her vision (Fig. 1). Major joints showed contractures. She was wasted secondary to her cGVHD as evidenced by a normal albumin level (3.7). Pentostatin was added to her regimen following the discontinuation of mycophenolate mofetil at 4 mg/m² per dose every 2 weeks for 6 months, followed by dosing

every 4 weeks. Eighteen months following initiation of pentostatin, she continues to show improvement. She has been tapered off other immunosuppressive medication except for cyclosporin. Her skin has softened. Her hyperpigmentation is resolving. Range of motion has improved in her shoulder and wrist joints. Her eyelids are no longer everted, allowing good vision (Fig. 1). She has not had any toxicity, including significant infections.

Patient 2

A 9-year-old girl with relapsed acute lymphocytic leukemia (ALL) underwent an HLA-matched related allogeneic bone marrow transplant following a conditioning regimen of cyclophosphamide and total body irradiation and GVHD prophylaxis with cyclosporin. Grade 1 acute skin GVHD was successfully treated with steroids, cyclosporin, and daclizumab.

Two months after discontinuation of immunosuppressives, she developed cGVHD. Thrombocytopenia with a platelet count of 80,000/mm³, oral dryness, and progressive skin involvement, including sclerodermatous, fascial, and hyperpigmentation changes, and limited range of motion were noted. Prednisone, FK506, and hydroxychloroquine caused transient improvement, but eventually her scleroderma, fasciitis, and decreased range of motion became debilitating. She was treated with a high-dose steroid pulse followed by pentostatin (4 mg/m² per dose) every 2 weeks for 6 months. Three months into pentostatin therapy, her steroids were completely weaned. She is currently 8 months off therapy with pentostatin and off all immunosuppressives. Other than minor contractures, cGVHD is inactive and she has full range of motion of all extremities.

Patient 3

A 7-year-old boy underwent an HLA-matched unrelated donor bone marrow transplant for relapsed ALL. His preparative regimen consisted of cyclophosphamide, total body irradiation, and thiopeta. GVHD prophylaxis consisted of cyclosporin and methylprednisolone. On day 34 the patient developed grade III acute GVHD involving his skin; it slowly improved but did not resolve over several weeks. One year after the transplant, he developed cGVHD of the skin with progressive sclerosis involving his abdomen, trunk, and upper extremities, and decreased range of motion of his joints. He was treated with steroids, thalidomide, hydroxychloroquine, and mycophenolate mofetil without improvement. His platelet count was 253,000/mm³ when he was diagnosed with cGVHD. His symptoms did not significantly improve on these medications. He was subsequently treated with pentostatin (4 mg/m² per dose) every 2 weeks for 6 months, followed by every 3 to 4 weeks for another 6 months. After 6 months of pentostatin treatment, the sclerodermatous changes of his skin and his range of motion were much improved. A year after starting pentostatin, cGVHD was completely inactive and all his immunosuppressives



FIGURE 1. (A) Patient 1 at initiation of pentostatin therapy. Eyelids are retracted. Stiffness of facial skin restricts expression. **(B)** Same patient 15 months after initiation of pentostatin therapy. Eyelids are improved. Facial skin has loosened enough to allow patient to smile.

were discontinued with no cGVHD flares. He had no significant toxicity during his course of pentostatin.

Patient 4

A 6-year-old boy was treated with a one-antigen-mismatched allogeneic bone marrow transplant for relapsed acute promyelocytic leukemia. On day 13, he developed grade 2 acute GVHD of the skin and gastrointestinal tract. He had improvement but not complete resolution of symptoms on steroids, mycophenolate mofetil, FK506, and daclizumab. Approximately 8 months after the transplant, while receiving mycophenolate mofetil and daclizumab, he developed progressive cutaneous cGVHD with multiple areas of scleroderma. He also developed mild thrombocytopenia with a platelet count of $145,000/\text{mm}^3$. Pentostatin was initiated at a dose of $2 \text{ mg}/\text{m}^2$ per dose weekly. Six weeks later the dosage was switched to $4 \text{ mg}/\text{m}^2$ per dose every other week. On this latter dose, his skin softened within 2 months. Six months after the increase in dose, pentostatin was discontinued because his progress had plateaued. One year later, he returned to our clinic with continued dry, flaky skin but no progression of GVHD, and he was off all im-

munosuppression. During his pentostatin course the patient had several episodes of sinusitis but no other toxicity.

Patient 5

A 12-year-old girl underwent an HLA-matched allogeneic bone marrow transplant for paroxysmal nocturnal hemoglobinuria. The preparative regimen consisted of cyclophosphamide and total body irradiation. Secondary to poor engraftment, she received a peripheral stem cell boost without a further preparative regimen 2 months after the transplant. GVHD prophylaxis was cyclosporine and prednisone. On day 100, following a steroid taper, she developed oral and hepatic cGVHD associated with a platelet count of $89,000/\text{mm}^3$. She was treated with FK506. After an initial improvement, her immunosuppressives were tapered off 1 month after development of cGVHD. Following this taper, her GVHD progressed to the skin with areas of hypo- and hyperpigmentation and limited extension of shoulders, elbows, and hips. She also developed diarrhea, and an endoscopy was suggestive of GVHD. Treatment with thalidomide and photopheresis produced a temporary improvement. Mycophenolate mofetil, FK506, hydroxychloroquine, and uli-

mately daclizumab were then added to her therapy following discontinuation of thalidomide. She had improvement of her scleroderma, but a month after weaning all immunosuppressives, she once again flared with whole-body erythema and scleroderma.

One month following this flare she was started on pentostatin 4 mg/m² biweekly for 6 months. On the pentostatin, her skin softened, she regained range of motion of joints and extremities, and some of the sores on her legs healed. During her treatment course, she developed worsening of her recurring gastrointestinal complaints, including postprandial abdominal pain and nausea. While it was thought that the pentostatin was not causal, it was temporarily discontinued but then restarted after her abdominal symptoms did not change. She is currently receiving pentostatin every 3

weeks, with continued improvement of the cGVHD of her skin.

Overall results are shown in Tables 1 and 2.

DISCUSSION

The incidence of cGVHD is approximately 24% in children receiving allogeneic stem cell transplantation.² The incidence may be higher in some groups of patients, such as those receiving mismatched or unrelated donor grafts, boosts for poor graft function, or peripheral blood stem cells.⁹ Although many patients respond to corticosteroids or cyclosporin, a significant number of children do not respond or the cGVHD flares during immunosuppression weaning. Moreover, protracted steroid therapy in children produces

TABLE 1.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age at cGVHD diagnosis	2 years	9 years	7 years	6 years	12 years
Sex	F	F	M	M	F
Diagnosis	Thalassemia major	ALL	ALL	APML	PNH
Prior treatment	Steroids–15 mg qd FK506–2.5 mg bid MMF–250 mg bid HCQ–75 mg bid	Steroids–30 mg qod FK506–1 mg bid qod HCQ–300 mg qd	Steroids–50 mg qd MMF–300 mg bid Thalidomide 550 mg qd HCQ–200 mg qd	Steroids–17.5 mg tid MMF–1500 mg IV bid Daclizumab–25 mg qwk	Steroids–30 mg qd FK506–1 mg qid MMF–500 mg bid Thalidomide–150 mg qd Photopheresis Daclizumab–75 mg q2wk HCQ–600 mg qd
Symptoms at initiation	Multiple areas of hyper/hypopigmentation Multiple areas of sclerodermatous skin Eyelids retracted Limited range of motion of all major joints Karnofsky = 60%	Lichenoid/erythematous rash over 50–75% of skin Hidebound skin, unable to pinch in multiple areas Diffuse areas of hyperpigmentation Limited range of motion of most joints Karnofsky = 70%	Diffuse hyperpigmentation, esp. over upper half of body Many areas of skin bound down Food sensitivity Limited range of motion of upper half of body Karnofsky = 70%	Lichenoid skin changes over entire body Hyperpigmented face Karnofsky = 80%	Lichenoid/erythematous rash over upper half of body Food sensitivity Lichenoid changes in oral mucosa Hyper/hypopigmentation changes Karnofsky = 70%
Time on pentostatin	18 months	6 months	1 year	6 months	6 months
Time since discontinuation	Not discontinued	7 months	8 months	16 months	Not discontinued
Symptoms at follow-up	Pigmentation changes improved, but present Fewer areas of sclerodermatous skin Eyelids no longer retracted Improved mobility of shoulder and wrist joints Karnofsky = 80%	Thickened skin with pockets of normal skin Hyperpigmented areas on lower extremities Minor contractures Full range of motion of all joints Karnofsky = 80%	Thickened skin with pockets of normal skin Tight fascia with normal areas Hyperpigmentation improved but present Limited range of motion of ankles, wrists; improved in upper body Karnofsky = 80%	Generalized dryness over scalp, palms, soles Karnofsky = 90%	Lichenoid/erythematous rash over <25% of skin Pigmentation changes persist Karnofsky = 80%

cGVHD, chronic graft-versus-host disease; FK506, tacrolimus; MMF, mycophenolate mofetil; HCQ, hydroxychloroquine; qd, daily; bid, twice daily; qod, every other day; tid, three times daily; qwk, once weekly, q2wk, once every other week; ALL, acute lymphoblastic leukemia; APML, acute promyelocytic leukemia; PNH, paroxysmal nocturnal hemoglobinuria.

TABLE 2. Duration of chronic graft-versus-host disease treatments before initiation of pentostatin

Case	Prednisone	FK506	MMF	HCQ	Daclizumab	Thalidomide	Photopheresis
1	15 months	9 months*	4 months	3 months	na	na	na
2	4 months*	5 months*	na	2 months*	na	na	na
3	12 months*	na	10 months*	2 months	na	6 months	na
4	3 months	na	8 months	na	4 months	na	na
5	20 months	20 months	13 months	12 months	8 months	8 months	8 cycles

*Indicates patient still on medication concurrently with pentostatin. na, not applicable.

unacceptable side effects. Chronic GVHD can cause permanent damage to almost any organ of the body and can be permanently disfiguring, presenting a significant problem to children because of long-term morbidity.¹⁰ New and more effective treatments for cGVHD with less toxicity are needed.

In our series, every child treated to date with pentostatin demonstrated a significant improvement in skin symptoms, with improvement in both lichenoid and sclerodermatous involvement. Every patient with contractures demonstrated at least a partial improvement in range of motion. The effects on pigmentation changes were less consistent. Four of the five patients continued to have pigmentation changes following their course of pentostatin. However, in three of these patients, either the total surface area or intensity was decreased.

Oral GVHD symptoms completely resolved with pentostatin in the two affected patients. This result is significant because oral GVHD symptoms are often severe enough to either reduce or prevent oral intake of food.

Our early experience with treating children with pentostatin has been encouraging, with dramatic improvement of the most serious symptoms and an enhanced quality of life in every patient. We attribute this improvement to pentostatin because it was the only new drug added to the patients' immunosuppressive regimen.

None of our patients experienced significant infections that were attributed to immunosuppression resulting from pentostatin therapy. Mild nausea/vomiting responsive to antiemetics and fatigue affected most of our patients at various stages of treatment. Gastrointestinal symptoms prompted discontinuation of the drug in only one patient (patient 5), who suffered unrelated gastrointestinal symptoms that were possibly complicated by nausea secondary to pentostatin.

While the pediatric experience with pentostatin as a treatment from cGVHD is small, the results achieved so far are encouraging. Thus far, pentostatin has only been used to treat cGVHD refractory to other therapies. Given the long-term sequelae of protracted steroid use, a non-steroid-containing regimen for cGVHD is desirable. Although a larger experience with pentostatin is clearly needed, if additional studies confirm the encouraging results in this small number of patients, a trial of pentostatin as front-line therapy may be indicated.

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