Narrowband ultraviolet B phototherapy for the treatment of steroid-refractory and steroid-dependent acute graft-versus-host disease of the skin

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Background: Acute graft-versus-host disease (aGvHD) is a common complication of allogeneic stem cell transplantation. It is usually treated with high doses of corticosteroids and other immunosuppressive agents. When cutaneous features are predominant, narrowband ultraviolet B (NB-UVB) phototherapy may be an attractive option for its steroid-sparing effect.

Objective: We sought to examine the clinical efficacy of NB-UVB in the treatment of steroid-refractory and steroid-dependent cutaneous aGvHD.

Methods: We conducted a retrospective chart review of patients with steroid-refractory and steroid-dependent aGvHD, who received NB-UVB between 2005 and 2009 at our institution.

Results: We identified 14 patients with aGvHD treated with NB-UVB between 2005 and 2009. The median number of treatments was 15, administered over a median of 43 days. Eight of 14 patients (57%) achieved a complete response at the end of treatment; an additional 3 patients (21%) achieved a partial response; and 3 patients (21%) showed no improvement at the time when phototherapy was discontinued (nonresponders). Four patients developed chronic graft-versus-host disease (GvHD). Three of the 8 complete responders remained free of GvHD at 6 months' follow-up.

Limitations: The rarity of steroid-refractory aGvHD limited the study to a small number of participants. Because GvHD is variable in its presentation and course, and life-threatening in many cases, large controlled prospective trials for potential therapies are difficult.

Conclusions: NB-UVB is a viable option for the treatment of steroid-refractory and steroid-dependent aGvHD of the skin. (J Am Acad Dermatol 2011;65:733-8.)

Key words: graft-versus-host disease; narrowband ultraviolet B; phototherapy; skin; steroid-refractory; ultraviolet light.

Acute graft-versus-host disease (aGvHD) is a major complication in more than 50% of patients receiving allogeneic stem cell transplantation.[1] Graft-versus-host reactions occur when donor immunocompetent cells attack the tissue of the recipient. Graft-versus-host disease (GvHD) is classified as acute or chronic, with the development of aGvHD being a risk factor for the development of chronic GvHD. The skin is often the first organ affected by aGvHD, which initially manifests as a papular eruption but can progress to desquamation resembling toxic epidermal necrolysis. Typically, aGvHD develops between 2 and 6 weeks after

Abbreviations used:

aGvHD:	acute graft-versus-host disease
GvHD:	graft-versus-host disease
NB-UVB:	narrowband ultraviolet B
PUVA:	psoralen plus ultraviolet A
UV:	ultraviolet

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transplantation. Chronic GvHD is characterized by lichenoid or sclerodermatous lesions of the skin. In many patients, GvHD is associated with significant morbidity and mortality.[2]

The currently accepted model for the pathophysiology of cutaneous aGvHD is described in 3 phases.[3] During the first phase, the conditioning regimen that the recipient patient undergoes before stem cell transplantation causes keratinocyte injury, resulting in a cytokine response that activates antigen-presenting epidermal dendritic (Langerhans) cells. In the second phase, antigen presentation results in activation of donor T cells and the production of cytokines within the Th1 pathway. The final step is host keratinocyte necrosis and apoptosis mediated by donor cytotoxic T cells. The established strategy for treatment of GvHD involves rapid control with high-dose systemic corticosteroids and long-term use of steroid-sparing immunosuppressive agents such as cyclosporine or tacrolimus.[4] If aGvHD does not respond to high-dose corticosteroids, it is designated "steroid-refractory" aGvHD. If aGvHD clears with high-dose systemic corticosteroids, but recrudesces on taper of steroids, it is designated "steroid-dependent" aGvHD. Unfortunately, in addition to toxicities associated with systemic steroid-sparing agents (eg, nephrotoxicity and neuropathy), the immunosuppression resulting from therapy (in addition to the immune dysregulation in the posttransplantation patient with GvHD) increases the risk of opportunistic infections, recurrent malignancy, secondary malignancies, and ultimately, death.[2,3,5]

When skin involvement is the predominant feature of aGvHD, there is an opportunity to administer skin-directed therapy with ultraviolet (UV) light. The immunomodulating effects of UV irradiation may allow for the reduction or replacement of standard systemic immunosuppressive therapy. After the Food and Drug Administration approval of psoralen plus UVA (PUVA) in 1982 for psoriasis and vitiligo, PUVA has been used to treat a variety of skin diseases, including GvHD.[6] More recent studies relate the efficacy of PUVA in treating GvHD,[7-9] and PUVA has become the standard of care with respect to skin-directed therapy for GvHD despite the theoretical risk of skin cancer and potential hepatotoxicity as a result of oral psoralen use.[10-12] Claims of greater long-term safety of narrowband UVB (NB-UVB) in comparison with PUVA has prompted the use of NB-UVB in treating cutaneous GvHD.[13] It is purported that NB-UVB therapy has a smaller risk of inducing skin cancer when compared with PUVA, even in patients requiring phototherapy for many years,[14] although this has not been substantiated in long-term studies, or in patients with allogeneic stem cell transplantation.

NB-UVB's efficacy in treating inflammatory disorders of the skin is likely derived from its antiproliferative and immunosuppressive effects. NB-UVB therapy suppresses the type 1 pathway (interleukin-12, interferon-γ, and interleukin-8), leads to apoptosis of skin-homing lymphocytes, increases the number of p53-positive epidermal cells, and reduces the number of Langerhans cells present in the epidermis and dermis.[15,16] These actions are likely critical to its effectiveness in treating cutaneous aGvHD, although studies on NB-UVB's mechanism of action in this relatively rare disease are lacking to date.

CAPSULE SUMMARY

- We retrospectively reviewed our institution's experience in treating 14 patients with steroid-refractory and steroid-dependent acute graft-versus-host disease using narrowband ultraviolet (UV) B.
- Eleven of 14 patients had a reduction in clinical staging of acute graft-versus-host disease with narrowband UVB therapy.
- No patients experienced side effects causing them to discontinue phototherapy.
- Narrowband UVB may be an attractive alternative to psoralen plus UVA in the treatment of cutaneous acute graft-versus-host disease, especially in those patients intolerant of oral psoralen.

METHODS

This report describes our center's experience with NB-UVB phototherapy in the treatment of steroid-refractory and steroid-dependent aGvHD of the skin between 2005 and 2009. This retrospective study was conducted under the approval of the Johns Hopkins Hospital Institutional Review Board.

Data collection

We retrospectively reviewed the records of patients with steroid-refractory and steroid-dependent aGvHD, who were treated with NB-UVB at the our hospital between January 2005 and August 2009. Patients were eligible for skin-directed therapy when they had skin-only disease or the extracutaneous aGvHD was either under good control or stable. Patients with chronic GvHD were excluded from this study. We collected data on patient demographics, malignancy diagnosis, donor source, conditioning