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Report

National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group Report

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A B S T R A C T

The 2006 National Institutes of Health (NIH) Consensus paper presented recommendations by the Ancillary Therapy and Supportive Care Working Group to support clinical research trials in chronic graft-versus-host disease (GVHD). Topics covered in that inaugural effort included the prevention and management of infections and common complications of chronic GVHD, as well as recommendations for patient education and appropriate follow-up. Given the new literature that has emerged during the past 8 years, we made further organ-specific refinements to these guidelines. Minimum frequencies are suggested for monitoring key parameters relevant to chronic GVHD during systemic immunosuppressive therapy and, thereafter, referral to existing late effects consensus guidelines is advised. Using the framework of the prior consensus, the 2014 NIH recommendations are organized by organ or other relevant systems and graded according to the strength and quality of supporting evidence.

INTRODUCTION

Chronic graft-versus-host disease (GVHD) is characterized by pleomorphic clinical manifestations with varying severity and clinical course. Prolonged systemic immunosuppressive treatment, including corticosteroids, is necessary to control disease severity and decrease the risk of nonrelapse mortality. Disease and treatment targeting the immune system causes delayed immune reconstitution with a high risk of infections and other related complications. Furthermore, the refractory nature of underlying fibrosis and limited success of systemic immunomodulatory treatments lead to significant persistence of morbidity for prolonged

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periods of time. Thus, ancillary therapy and supportive care become central components in the long-term management of chronic GVHD after allogeneic hematopoietic cell transplantation (HCT).

As in the 2005 National Institutes of Health (NIH) consensus framework, "ancillary therapy and supportive care" embraces the most frequent topical immunosuppressive or anti-inflammatory interventions and any other interventions directed at organ-specific control of symptoms or complications resulting from GVHD and its therapy. Also included in this definition are educational, preventive, and psychosocial interventions with this same objective. Several important aspects of good follow-up care, such as monitoring for and management of certain medication toxicities (eg, hypertension, hyperlipidemia, renal dysfunction, seizures, etc.) and problems not directly related to chronic GVHD (eg, iron overload, psychosocial adaptation) fall outside the scope of this document. General screening and preventive policies for survivors of HCT are summarized elsewhere [1,2].

METHODS

The working group searched the Medline (PubMed) database using a broad search strategy to identify studies related to prevention and management of infections, vaccinations, and common complications of chronic GVHD, patient education, and appropriate long-term follow-up and monitoring. The primary search was conducted using "graft-versus-host disease," "chronic," "blood and marrow transplantation," and a variety of specific terms to capture pertinent organ-specific focus (eg, "ocular," "oral," etc.). Relevant references in the publications were also reviewed. In general, studies with cohorts including fewer than 20 patients, case reports, and studies of agents that are not commercially available were excluded from consideration.

Recommendations are organized according to an evidence-based system to reflect the strength of recommendations and the quality of evidence supporting them (Appendix 1). A version of this document posted on the Internet includes hyperlinks to Supplements 2-11 that provide additional organ-specific dispensary and other relevant information.

The 2014 international NIH Ancillary Therapy and Supportive Care Working Group was first subdivided into organ-specific subgroups, each of which was charged with the purpose of reviewing all new evidence since 2005. The subgroups subsequently came together to discuss all relevant new findings. Final recommendations were developed after discussion with the steering committee (Appendix 2). Overall, the percentages of level I and II evidence-based recommendations have not changed from 2006 to 2014 (Figure 1).

A summary of the major changes to the 2006 NIH Ancillary and Supportive Care Consensus Recommendations is shown in Supplement 1. The Working Group emphasizes that the recommendations in this document represent a wide variety of generally accepted current medical practices. Good clinical judgment and individual circumstances should determine appropriate interventions for specific patients.

SUMMARY OF RECOMMENDATIONS

Table 1 provides a summary of ancillary therapy and supportive care interventions, categorized by organ system. Table 2 provides a summary of general monitoring recommended for patients diagnosed with chronic GVHD.

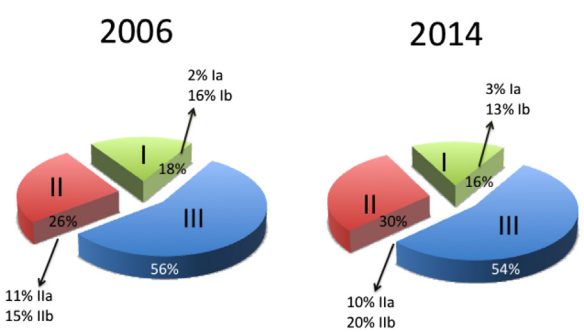

Figure 1. Distribution of NIH Consensus Ancillary and Supportive Care Recommendations based on quality of evidence compared to 2006 Consensus. The number of recommendations made in 2006 was 100 and in 2014, it was 123.

SKIN AND APPENDAGES

Ancillary and supportive care of the skin and appendages focuses on prevention, management of manifestations such as pruritus, rash, pain, dyspigmentation and limited range of motion (ROM), as well as topical care for erosions, ulcerations, and superinfection (Table 3). Topical therapy plays an important role in alleviating symptoms and treating complications caused by loss of skin integrity and immunosuppression. Because skin cancer incidence is increased in patients with chronic GVHD, vigilant monitoring is necessary so that early malignancies and premalignancies can be detected early and treated appropriately.

Measures to Prevent the Development or Exacerbation of GVHD

Environmental ultraviolet radiation can cause exacerbation of cutaneous GVHD [5]. Photoprotection includes protective clothing, sun avoidance, physical sunblocks, and sunscreens. Topically applied agents should protect against both ultraviolet A (UVA) and ultraviolet B (UVB). Micronized zinc, micronized titanium dioxide, mexoryl SX, or Parsol 1789 (avobenzone; DSM, Basel, Switzerland) are useful additives to ensure adequate UVA protection. Laundry rinse cycle additives can enhance the ultraviolet barrier function of clothing.

Avoidance of Photosensitizing Agents

Several commonly prescribed medications have been associated with phototoxic drug eruptions that typically appear like severe sunburn, often associated with skin burning and/or pruritus. This list of such medications is extensive but voriconazole deserves special mention because of its particular dual association with phototoxicity and increased risk of squamous cell carcinoma [6].

Topical Care and Therapies for Intact Skin

Most patients with extensive rash will require systemic therapy, a topic beyond the scope of this review.

Regular lubrication of dry but intact skin with emollients may decrease pruritus and maintain skin integrity. Ointments and creams are better skin softeners than lotions and are less likely to sting when applied to erythematous skin. Moisturizers that contain 3% to 10% urea or glycerol are particularly efficacious for increasing skin hydration, but urea products can be more irritating to inflamed skin or in infants.

Topical steroids and emollients can improve cutaneous chronic GVHD, particularly nonsclerotic skin lesions without erosions or ulcerations (lichen-planus–like or papulosquamous plaques). Long-term use of topical steroids may be complicated by local skin atrophy and development of striae.

1. General guidelines regarding topical steroid recommendations for skin GVHD:
   a. From the neck down: treatment should begin with mid-strength topical steroids (eg, triamcinolone 0.1% cream or ointment). In unresponsive cases, short-term occlusion of mid-strength steroids with damp towels ("wet wraps") increases skin hydration and steroid penetration. When this is impractical, higher potency steroids (eg,