Journal of Bone Marrow Research
ISSN: 2329-8820

Sousa and Herskovitz, J Bone Marrow Res 2013, 1:4
DOI: 10.4172/2329-8820.1000134

Review Article Open Access

Skin Signs of Graft Versus Host Disease

Isabel Cristina Valente Duarte de Sousa[1*] and Ingrid Herskovitz[2]

[1]Centro Médico ABC Santa Fé, Mexico
[2]University of Miami Dermatology and Cutaneous Surgery Department, Mexico

Abstract

Graft-versus-host disease is a common complication of allogenic hematopoietic cell transplantation and less frequently of solid organ transplantation. The skin is one of the initial and main organs affected, and as such, recognizing the dermatologic manifestations allows early diagnosis and treatment.

In this article we aim to describe the cutaneous manifestations of graft-versus-host disease so that non-dermatologist is able to recognize the early signs of this complication.

Keywords: Graft-versus-host disease; Acute graft-versus-host disease; Chronic graft-versus-host disease; Scleromatous graft-versus-host disease; Lichen planus-like graft-versus-host disease

Introduction

Graft-Versus-Host Disease (GVHD) is a common complication associated with high mortality that results from the immunologic insult of introducing immunologically competent cells into an immunoincompetent host, which allows these grafted cells to mount a destructive immune response against the recipient tissues [1-9].

The main cause of GVHD is allogenic Hematopoietic Cell Transplantation (HCT) [10,11] although it can also be seen secondary to solid organ transplantation [11-14].

The skin is one of the initial and main organs affected by GVHD in up to 94.2% of patients [1,7,8,10,11,15], and as such, recognizing these dermatologic manifestations represents an important tool for early diagnosis allowing prompt installation of treatment, although an early start to therapy is not always determinant of outcome [16].

Historically, GVHD has been divided into acute GVHD (aGVHD) and chronic GVHD (cGVHD) [3,10]. Acute GVHD describes a distinctive syndrome of dermatitis, bilirubin elevation, and diarrea developing within 100 days of transplantation [1,3,10] Chronic GVHD describes a more diverse syndrome developing after day 100 [2-4,10]. However, this definition falls short, and in 2005 the National Institutes of Health classification included late-onset acute GVHD (after day 100) and an overlap syndrome with features of both acute and chronic GVHD [17].

In this article we aim to describe the cutaneous manifestations GVHD so that non-dermatologist are able to recognize the early signs of this complication.

Risk Factors

Because GVHD results from the recognition of host tissues as foreign by immunocompetent donor cells, the risk of GVHD increases with greater HLA disparity between the donor and recipient [1,18,19]. However, it is important to mention that despite HLA matching between donor and receiver, 40% of patients still develop GVHD due to the genetic differences of minor histocompatibility antigens [1].

Another recognized risk factor is the recipient's age because the risk of GVHD seems to rise with increasing age [1,16].

Human herpesvirus type 6 reactivation is significantly associated with the occurrence of GVHD, as is coinfection with Epstein-Barr virus [20].

Acute Graft Versus Host Disease

The incidence of acute GVHD varies between 20% and 70%, based on histocompatibility differences between the donor and recipient, the age of the recipient, the type of inmunosupression regimen, and the stage of primary disease [3,10].

Acute GVHD usually starts as pruritic and sometimes painfull erythematous-purpuric maculopapular exantema [16] on the palms, soles, cheeks, neck, ears and upper trunk, preferentially around the hair follicles [10,16]. The scalp is usually spared [1]. As the severity of the GVHD increases, the exantema progresses and can affect the total body surface area [10]. Erythroderma, vesicles, bullae and a positive Nikolsky's sign define the most severe form of acute GVHD [1,10,21].

Based on the cutaneous involvement in aGVHD a staging system has been proposed to determine the severity of the disease, where Grade 0 represents the absence of rash related to GVHD, Grade 1 represent a maculopapular rash affecting less than 25% of total body surface area, Grade 2 represents a maculopapular rash that affects 25-50% of total body surface area, Grade 3 represents a macular, papular or vesicular eruption affecting between 50% to 100% of total body surface area and Grade 4 represents a generalized exfoliative dermatitis, ulcerative dermatitis or bullae [22].

After the skin, the next most frequently involved organs in acute GVHD are the liver and the gastrointestinal tract, where the disease causes asymptomatic elevation of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, nausea, vomiting and diarrhea [22].

Chronic Graft Versus Host Disease

Chronic GVHD may occur as either a late phase of acute GVHD or as a distinct entity and it may affect up to 30-80% of patients after

***Corresponding authors:** Isabel Cristina Valente Duarte de Sousa, Centro Médico ABC Santa Fé, Avenida Carlos Graff Fernández 154, consultorio 343, Colonia Tlaxcala, Cuajimalpa, Mexico DF, México, CP 05300, Tel: +525516647004; E-mail: cristinavalente@me.com

Received May 21, 2013; **Accepted** June 15, 2013; **Published** November 18, 2013

Citation: Sousa IC, Herskovitz I (2013) Skin Signs of Graft Versus Host Disease. J Bone Marrow Res 1: 134. doi: 10.4172/2329-8820.1000134

allogenic stem cell transplantation [1,3,4,10,23].

The skin is the primary organ involved in chronic GVHD followed by the oral mucosa, the liver and the eye [10,24].

The cutaneous lesions have been classically divided into two categories: lichen planus-like and scleroderma-like [7]. However, the clinical spectrum of cGVHD is broad [25,26] and it can include poikiloderma, xerosis, annular scleroderma-like lesions, keratosis pilaris-like lesions, psoriasiform lesiones, deep sclerotic features, eccema-like lesions, acral erythema, fasciitis, morphea-like superficial sclerotic features, and/or lichen sclerosus-like [1,7,10,24,27].

The first indication of cGVHD is the appearance of focal, folliculocentric, confluent or linear violaceous lichenified papules, vesicles and plaques that arise with a predilection for flexural surfaces [28]. White lacy patches, indistinguishable from those present in oral lichen planus, can appear on the oral mucosal [10]. Other oral symptoms include xerostomia, mucocele, mucosal atrophy and ulcers [17].

Sclerodermatous GVHD is characterized by hypo or hyperpigmented thickened, tight, indurated and fragile skin which is often associated with poor wound-healing, inadequate lymphatic drainage, skin ulcers from minor trauma, contractures and limited joint mobility [10,24,25]. Characteristically, these lesions tend to appear on sites of minor skin trauma or pressure (waistband line, brassiere line) or on sites of previous skin damage (such as old scars or site of a previous herpes zoster infection) [10].

Extensive skin involvement (>50% of body surface area) [28] is associated with poor prognosis and an increased risk of transplant-related mortality and as well as non-relapse mortality (NRM) in patients with cGVHD [3,24].

Other mucocutaneous manifestations of cGVHD secondary to dermal sclerosis are scarring and non-scarring alopecia, nail dystrophy (in up to 50% of patients), nail pterygium, onycholysis, loss of adnexal structures such as sweat glands, calcinosis, stenosis of the vagina and vulva and xerostomy similar to those observed in systemic skin sclerosis [10,29]. However, unlike systemic sclerosis, involvement of the face, sclerodactyly and Raynaud phenomenon are uncommon [10].

Histology

Skin biopsy with routine hematoxylin and eosin staining is the primary tool for evaluating skin eruptions in suspected acute and chronic GVHD [30].

Acute GVHD is characterized by an interphase dermatitis with vacuolar degeneration due to apoptosis of the basal layer, dyskeratotic and necrotic keratonicytes, exocytosis of lymphocytes and perivascular infiltration in the dermis [1,26,31,32]. Depending on the histological findings a scaling system has been proposed, where Grade 1 consist of lymphocytic infiltrates in the upper dermis without epidermal changes, Grade 2 presents with vacuolization of the basal layer and dyskeratotic keratonocytes, Grade 3 consist of subepidermal vesicle formation and Grade 4 corresponds to complete dermal and epidermal separation with massive necrosis of keratinocytes [10,32,33].

Chronic GVHD on the other hand has unremarkable epidermal changes or similar changes than those observed in aGVHD, but most importantly it presents with thickened and homogenized collagen bundles that affect the dermis, the adipose tissue and even de fascia [7,26].

Differential Diagnosis

The diagnosis of GVHD is complicated by the complex immune status of the patient and by the fact that other eruptions that are common in immunosupressed patients can be easily confused with GVHD [34]. An accurate diagnosis can be achieved by using specific histological and immunohistochemical criteria [35-37].

Differential diagnosis of skin symptoms includes engraftment syndrome, toxic epidermal necrolysis, irritant or allergic contact dermatitis, lichen planus, morphea, scleroderma, erythroderma, toxic shock syndrome, stevens-johnson syndrome, staphylococcal scalded skin syndrome and most commonly and importantly drug eruptions and viral exanthemas [34,38]. Drug-induced rashes are very common in post-transplant patients due to the amount of medications that these patients have to take. Alemtuzumab used as a conditioning regimen in a patient treated for chronic lymphocytic leukemia with autologous stem cell transplantation, has been associated with a GVHD-like rash [39].

Prevention and Treatment

The best treatment for graft versus host disease (GVHD) is prevention [40]. The current main measures to prevent and treat GVHD are the application of cytotoxic drugs (such as cyclosporine A), immunosuppressive agents (mainly high-dose steroids), and removal of T cells in graft before and after transplantation [5,41,42]. Anti-T-cell globulin, when added to standard immunosuppressive prophylaxis, can result in decreased incidence of acute and chronic GVHD [43].

Treatment has to be multidisciplinary with many specialists involved in the care of the patient [44].

Topical steroids, such as triamcinolone or clobetasol ointment, can be used as a first line treatment in acute GVHD stages I and II [7,31]. For oral lesions, topical tacrolimus has been used effectively [45].

Systemic therapy is recommended in all cases of grade III-IV acute GVHD and chronic GVHD [46,47]. The percentage of body surface area affected and depth of sclerotic involvement in chronic scleromatous GVHD are key determinants for administration of immunosuppressive therapy, its duration and intensity, treatment response, and impairment of patients' quality of life [46,48]. The most common first-line treatment is steroids in combination with cyclosporine or another calcineurin inhibitor [49].

For patients with steroid-resistant GvHD, second-line treatment is less well defined due to the lack of clinical studies [1,4,47]. There are numerous single drugs or combination therapies that can be used to treat steroid-resistant GvHD, including methotrexate, calcineurin inhibitors (such as tacrolimus, and sirolimus), pulses of high doses of methylprednisolone, extracorporeal photopheresis, mycophenolate mofetil, immunomodulating agents like thalidomide, azathioprine, rituximab, infliximab, daclizumab, hydroxychloroquine, imatinib, alemtuzumab, etanercept, UVA1 phototherapy, extracorporeal photochemotherapy, denileukin diftitox amongst others [4,27,47,50-70].

Broad antibiotic, antifungal and antiviral, prophylaxis is of the utmost importance, because infectious complications are common in GVHD [1,16].

Sclerodermatous changes of chronic GVHD may require surgical release of a contracted joint. Also, nonhealing-ulcers secondary to sclerodermatous GVHD may require wound debridement and skin grafting [50].

Conclusion

The skin the first organ affected by GVHD and as such, recognizing the early dermatologic manifestations can allow prompt diagnosis and treatment, which may prevent the progression to higher-grade disease and improve the outcome of patients [3].

Patients with significant skin involvement in GVHD have increased risk of infections, impaired functional performance, skin cancer, and psychological distress (depression and struggles with body image) and as such, dermatologists play an important role in the multidisciplinary team needed to treat these patients [50].

Unfortunately, current treatment strategies are still not 100% effective because the pathophysiology of GVHD is still not completely understood. As more research is made in this area, newer treatment options targeting the specific immunological disparities that occur in GVHD will become available.

References

1. Ferrara JL, Levine JE, Reddy P, Holler E (2009) Graft-versus-host disease. Lancet 373: 1550-1561.
2. Arai S, Jagasia M, Storer B, Chai X, Pidala J, et al. (2011) Global and organ-specific chronic graft-versus-host disease severity according to the 2005 NIH Consensus Criteria. Blood 118: 4242-4249.
3. Vargas-Díez E, García-Díez A, Marín A, Fernández-Herrera J (2005) Life-threatening graft-vs-host disease. Clin Dermatol 23: 285-300.
4. Gutiérrez-Aguirre CH, Cantú-Rodríguez OG, Borjas-Almaguer OD, González-Llano O, Jaime-Pérez JC, et al. (2012) Effectiveness of subcutaneous low-dose alemtuzumab and rituximab combination therapy for steroid-resistant chronic graft-versus-host disease. Haematologica 97: 717-722.
5. Cheng J, Zhou Y, Chen B, Wang J, Xia G, et al. (2011) Prevention of acute graft-versus-host disease by magnetic nanoparticles of Fe3O4 combined with cyclosporin A in murine models. Int J Nanomedicine 6: 2183-2189.
6. Socié G, Blazar BR (2009) Acute graft-versus-host disease: from the bench to the bedside. Blood 114: 4327-4336.
7. Alexander LJ, Paravar T, Duvic M, Prieto V, Hymes SR (2012) Annular plaques: An unusual manifestation of graft-versus-host disease. Dermatol Online J 18: 4.
8. Chaib E, Silva FD, Figueira ER, Lima FR, Andraus W, et al. (2011) Graft-versus-host disease after liver transplantation. Clinics (Sao Paulo) 66: 1115-1118.
9. Teshima T, Ferrara JL (2002) Understanding the alloresponse: new approaches to graft-versus-host disease prevention. Semin Hematol 39: 15-22.
10. Hymes SR, Alousi AM, Cowen EW (2012) Graft-versus-host disease: part I. Pathogenesis and clinical manifestations of graft-versus-host disease. J Am Acad Dermatol 66: 515.
11. Akbulut S, Yilmaz M, Yilmaz S (2012) Graft-versus-host disease after liver transplantation: a comprehensive literature review. World J Gastroenterol 18: 5240-5248.
12. Whalen JG, Jukic DM, English JC 3rd (2005) Rash and pancytopenia as initial manifestations of acute graft-versus-host disease after liver transplantation. J Am Acad Dermatol 52: 908-912.
13. Smith DM, Agura ED, Ausloos K, Ring WS, Domiati-Saad R, et al. (2006) Graft-vs-host disease as a complication of lung transplantation. J Heart Lung Transplant 25: 1175-1177.
14. Romagnuolo J, Jewell LD, Kneteman NM, Bain VG (2000) Graft-versus-host disease after liver transplantation complicated by systemic aspergillosis with pancarditis. Can J Gastroenterol 14: 637-640.
15. Akpek G, Lee SJ, Flowers ME, Pavletic SZ, Arora M, et al. (2003) Performance of a new clinical grading system for chronic graft-versus-host disease: a multicenter study. Blood 102: 802-809.
16. Deeg HJ (1994) Graft-versus-host disease and the development of late complications. Transfus Sci 15: 243-254.
17. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, et al. (2005) National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 11: 945-956.
18. Ferrara GB, Bacigalupo A, Lamparelli T, Lanino E, Delfino L, et al. (2001) Bone marrow transplantation from unrelated donors: the impact of mismatches with substitutions at position 116 of the human leukocyte antigen class I heavy chain. Blood 98: 3150-3155.
19. Flomenberg N, Baxter-Lowe LA, Confer D, Fernandez-Vina M, Filipovich A, et al. (2004) Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome. Blood 104: 1923-1930.
20. Hentrich M, Oruzio D, Jäger G, Schlemmer M, Schleuning M, et al. (2005) Impact of human herpesvirus-6 after haematopoietic stem cell transplantation. Br J Haematol 128: 66-72.
21. Schauder CS, Hymes SR, Rapini RP, Zipf TF (1992) Vesicular graft-versus-host disease. Int J Dermatol 31: 509-510.
22. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, et al. (1995) 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 15: 825-828.
23. Atkinson K (1990) Chronic graft-versus-host disease. Bone Marrow Transplant 5: 69-82.
24. Lee SJ, Klein JP, Barrett AJ, Ringden O, Antin JH, et al. (2002) Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. Blood 100: 406-414.
25. White JM, Creamer D, du Vivier AW, Pagliuca A, Ho AY, et al. (2007) Sclerodermatous graft-versus-host disease: clinical spectrum and therapeutic challenges. Br J Dermatol 156: 1032-1038.
26. Shulman HM, Kleiner D, Lee SJ, Morton T, Pavletic SZ et al. (2006) Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: II (Pathology Working Group Report). Biol Blood Marrow Transplant 12: 31-47.
27. Creamer D, Martyn-Simmons CL, Osborne G, Kenyon M, Salisbury JR, et al. (2007) Eczematoid graft-vs-host disease: a novel form of chronic cutaneous graft-vs-host disease and its response to psoralen UV-A therapy. Arch Dermatol 143: 1157-1162.
28. Beers B, Kalish RS, Kaye VN, Dahl MV (1993) Unilateral linear lichenoid eruption after bone marrow transplantation: an unmasking of tolerance to an abnormal keratinocyte clone? J Am Acad Dermatol 28: 888-892.
29. Schultz KR, Miklos DB, Fowler D, Cooke K, Shizuru J, et al. (2006) Toward biomarkers for chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: III. Biomarker Working Group Report. Biol Blood Marrow Transplant 12: 126-137.
30. Firoz BF, Lee SJ, Nghiem P, Qureshi AA (2006) Role of skin biopsy to confirm suspected acute graft-vs-host disease: results of decision analysis. Arch Dermatol 142: 175-182.
31. Brunengraber LN, Turner M, Lee CC, Stratton P (2011) Bilateral areolar lesions in a patient with acute cutaneous graft-vs-host disease. Arch Dermatol 147: 509-511.
32. Horn TD, Zahurak ML, Atkins D, Solomon AR, Vogelsang GB (1997). Lichen planus-like histopathologic characteristics in the cutaneous graft-vs-host reaction. Prognostic significance independent of time course after allogeneic bone marrow transplantation. Arch Dermatol 133: 961-965.
33. Lerner KG, Kao GF, Storb R, Buckner CD, Clift RA, et al. (1974) Histopathology of graft-vs.-host reaction (GvHR) in human recipients of marrow from HL-A-matched sibling donors. Transplant Proc 6: 367-371.
34. Inaba H, Hale G, Leung W, Woodard P, Burnette K, et al. (2006) Diagnostic challenge in recurrent skin rash after autologous bone marrow transplantation. J Pediatr Hematol Oncol 28: 525-528.
35. Volc-Platzer B, Rappersberger K, Mosberger I, Hinterberger W, Emminger-Schmidmeier W, et al. (1988) Sequential immunohistologic analysis of the skin following allogeneic bone marrow transplantation. J Invest Dermatol 91: 162-168.

36. Peck GL, Elias PM, Graw RG Jr (1972) Graft-versus-host reaction and toxic epidermal necrolysis. Lancet 2: 1151-1153.

37. Mazzaferro V, Andreola S, Regalia E, Poli F, Doci R, et al. (1993) Confirmation of graft-versus-host disease after liver transplantation by PCR HLA-typing. Transplantation 55: 423-425.

38. Kuskonmaz B, Güçer S, Boztepe G, Cetin M, Uckan D (2007) Atypical skin graft-vs.-host disease following bone marrow transplantation in an infant. Pediatr Transplant 11: 214-216.

39. Zenz T, Ritgen M, Dreger P, Kröber A, Barth TF, et al. (2006) Autologous graft-versus-host disease-like syndrome after an alemtuzumab-containing conditioning regimen and autologous stem cell transplantation for chronic lymphocytic leukemia. Blood 108: 2127-2130.

40. Lee SJ, Flowers ME (2008) Recognizing and managing chronic graft-versus-host disease. Hematology Am Soc Hematol Educ Program 134-141.

41. Roberts JP, Ascher NL, Lake J, Capper J, Purohit S, et al. (1991) Graft vs. host disease after liver transplantation in humans: a report of four cases. Hepatology 14: 274-281.

42. Collins RH Jr, Cooper B, Nikaein A, Klintmalm G, Fay JW (1992) Graft-versus-host disease in a liver transplant recipient. Ann Intern Med 116: 391-392.

43. Finke J, Bethge WA, Schmoor C, Ottinger HD, Stelljes M, et al. (2009) Standard graft-versus-host disease prophylaxis with or without anti-T-cell globulin in haematopoietic cell transplantation from matched unrelated donors: a randomised, open-label, multicentre phase 3 trial. Lancet Oncol 10: 855-864.

44. Wu PA, Cowen EW (2012) Cutaneous graft-versus-host disease--clinical considerations and management. Curr Probl Dermatol 43: 101-115.

45. Albert MH, Becker B, Schuster FR, Klein B, Binder V, et al. (2007) Oral graft vs. host disease in children--treatment with topical tacrolimus ointment. Pediatr Transplant 11: 306-311.

46. Lee SJ, Vogelsang G, Gilman A, Weisdorf DJ, Pavletic S, et al. (2002) A survey of diagnosis, management, and grading of chronic GVHD. Biol Blood Marrow Transplant 8: 32-39.

47. Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, et al. (2011) Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. Biol Blood Marrow Transplant 17: 1-17.

48. Vogelsang GB (2001) How I treat chronic graft-versus-host disease. Blood 97: 1196-1201.

49. Ferrara JL, Yanik G (2005) Acute graft versus host disease: pathophysiology, risk factors, and prevention strategies. Clin Adv Hematol Oncol 3: 415-419, 428.

50. Hymes SR, Alousi AM, Cowen EW (2012) Graft-versus-host disease: part II. Management of cutaneous graft-versus-host disease. J Am Acad Dermatol 66: 535.

51. Antin JH, Kim HT, Cutler C, Ho VT, Lee SJ, et al. (2003) Sirolimus, tacrolimus, and low-dose methotrexate for graft-versus-host disease prophylaxis in mismatched related donor or unrelated donor transplantation. Blood 102: 1601-1605.

52. Gómez-Almaguer D, Ruiz-Argüelles GJ, del Carmen Tarín-Arzaga L, González-Llano O, Gutiérrez-Aguirre H, et al. (2008) Alemtuzumab for the treatment of steroid-refractory acute graft-versus-host disease. Biol Blood Marrow Transplant 14: 10-15.

53. Kimby E (2005) Tolerability and safety of rituximab (MabThera). Cancer Treat Rev 31: 456-473.

54. Lopez F, Parker P, Nademanee A, Rodriguez R, Al-Kadhimi Z, et al. (2005) Efficacy of mycophenolate mofetil in the treatment of chronic graft-versus-host disease. Biol Blood Marrow Transplant 11: 307-313.

55. Kottaridis PD, Milligan DW, Chopra R, Chakraverty RK, Chakrabarti S, et al. (2000) In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. Blood 96: 2419-2425.

56. Chakraverty R, Orti G, Roughton M, Shen J, Fielding A, et al. (2010) Impact of in vivo alemtuzumab dose before reduced intensity conditioning and HLA-identical sibling stem cell transplantation: pharmacokinetics, GVHD, and immune reconstitution. Blood 116: 3080-3088.

57. Ruiz-Argüelles GJ, Gil-Beristain J, Magaña M, Ruiz-Delgado GJ (2008) Alemtuzumab-induced resolution of refractory cutaneous chronic graft-versus-host disease. Biol Blood Marrow Transplant 14: 7-9.

58. Teshima T, Nagafuji K, Henzan H, Miyamura K, Takase K, et al. (2009) Rituximab for the treatment of corticosteroid-refractory chronic graft-versus-host disease. Int J Hematol 90: 253-260.

59. Kharfan-Dabaja MA, Bazarbachi A (2010) Emerging role of CD20 blockade in allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 16: 1347-1354.

60. Grundmann-Kollmann M, Behrens S, Gruss C, Gottlöber P, Peter RU, et al. (2000) Chronic sclerodermic graft-versus-host disease refractory to immunosuppressive treatment responds to UVA1 phototherapy. J Am Acad Dermatol 42: 134-136.

61. Tseng S, Pak G, Washenik K, Pomeranz MK, Shupack JL (1996) Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. J Am Acad Dermatol 35: 969-979.

62. Patriarca F, Sperotto A, Damiani D, Morreale G, Bonifazi F, et al. (2004) Infliximab treatment for steroid-refractory acute graft-versus-host disease. Haematologica 89: 1352-1359.

63. Przepiorka D, Kernan NA, Ippoliti C, Papadopoulos EB, Giralt S, et al. (2000) Daclizumab, a humanized anti-interleukin-2 receptor alpha chain antibody, for treatment of acute graft-versus-host disease. Blood 95: 83-89.

64. Levine JE, Paczesny S, Mineishi S, Braun T, Choi SW, et al. (2008) Etanercept plus methylprednisolone as initial therapy for acute graft-versus-host disease. Blood 111: 2470-2475.

65. Alousi AM, Weisdorf DJ, Logan BR, Bolaños-Meade J, Carter S, et al. (2009) Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. Blood 114: 511-517.

66. Ho VT, Cutler C (2008) Current and novel therapies in acute GVHD. Best Pract Res Clin Haematol 21: 223-237.

67. Ho VT, Zahrieh D, Hochberg E, Micale E, Levin J, et al. (2004) Safety and efficacy of denileukin diftitox in patients with steroid-refractory acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Blood 104: 1224-1226.

68. Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, et al. (2009) Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood 114: 709-718.

69. Perfetti P, Carlier P, Strada P, Gualandi F, Occhini D, et al. (2008) Extracorporeal photopheresis for the treatment of steroid refractory acute GVHD. Bone Marrow Transplant 42: 609-617.

70. Flowers ME, Apperley JF, van Besien K, Elmaagacli A, Grigg A, et al. (2008) A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood 112: 2667-2674.