Leukemia (2005) 19, 1532–1535

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KEYNOTE ADDRESS

Chronic graft-versus-host disease: where is promise for the future?

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Leukemia (2005) **19,** 1532–1535. doi:10.1038/sj.leu.2403856; published online 30 June 2005

Introduction

Chronic graft-versus-host disease (GVHD) remains a troubling and dangerous complication of allogeneic stem cell transplantation with little prospect of a simple solution. The frequency of chronic GVHD over the last 12 years has increased. Data from the Fred Hutchinson Cancer Research Center indicate that in 1990, chronic GVHD incidence was about 40%; currently, the incidence is 65–80%.[1,2] This increase can be attributed to a greater number of patients surviving transplant, and to older patients being transplanted with unrelated or alternative donor grafts.[2] Even though chronic GVHD may promote graft-versus-leukemia effects, large observational studies have shown that chronic GVHD is still the leading cause of nonrelapse death 2 years after transplantation.[3] Patient selection plays an important role in the outcome of chronic GVHD treatment trials,[4] as demonstrated by widely varying response rates to prednisone, cyclosporine, azathioprine, or combination regimens.[5,6]

Chronic GVHD has been attributed to T-lymphocyte activation and overexpansion of autoreactive subsets, or both. Data from a large randomized trial in about 400 patients who received unrelated donor transplantation with either T-cell-depleted or unmodified grafts showed similar risks of chronic GVHD and nearly 20% chronic GVHD-related mortality (Pavletic SZ *et al*. *Blood* 2003; **102:** 154a; abstract). This incidence is similar to that for sibling donor transplants.[7–9] Only about 50% of those who developed chronic GHVD in this trial were alive at 3–4 years following the transplant. In general, neither unmodified grafts nor T-cell depletion alter the incidence of chronic GVHD or improve overall survival.

Preventing chronic GVHD

Treatment regimens intended to prevent chronic GVHD have included early administration of high- or low-dose cyclosporine and trials to determine the optimum duration of therapy. Extended cyclosporine therapy (24 months) was compared to a conventional 6-month course ($n=162$),[10] and 6 months to 60 days of cyclosporine therapy in patients with no active acute GVHD ($n=103$).[11] Extended therapy yielded no difference in outcomes.[10,11] Randomized trials have also evaluated cyclosporine and methotrexate with or without thalidomide and showed no difference in the resolution of chronic GVHD.[12–14] The addition of thalidomide to cyclosporine was hypothesized to pre-emptively treat chronic GVHD, but in fact it was associated with more acute GVHD and worse survival. In two randomized trials of intravenous (i.v.) immunoglobulin, one *vs* placebo ($n=250$) and one comparing several different dose levels that had been reportedly associated with reduced GVHD ($n=627$),[15] there was no difference in the incidence of chronic GVHD. Even though patients who develop chronic GVHD may have a lower risk of relapse, particularly those with mild-to-moderate disease, chronic GVHD substantially increases treatment-related mortality and regularly worsens disease-free survival.[16] There are no specific effective interventions at this time to prevent chronic GVHD.

Treating chronic GVHD

A major long-term morbidity of chronic GVHD is the ongoing need for prednisone or other immunosuppressive agents. One strategy is to control symptoms early, and then slowly taper patients off the immunosuppressants. In a study of 159 patients at the University of Minnesota, bolus steroid induction therapy was administered for 8 weeks followed by alternate day prednisone 0.5 mg/kg and cyclosporine. Patients were followed for a median of 8 (range 1–13) years. Of those who responded, about 2/3 did so in the first 6 months, with over 50% still responding at a year. GVHD flares occurred primarily within the first year (Table 1).[17] Although conventional steroids and cyclosporine can control chronic GVHD, additional continued immunosuppression is often needed. However, it is unclear that more intense immunosuppression will be more effective. Conventional predictors of favorable chronic GHVD (platelets $>100\,000/\mu$l, age <20 years, and the absence of gastrointestinal (GI) involvement) each independently indicate a greater likelihood of a good response to initial therapy. In patients with *de novo* chronic GVHD or quiescent chronic GVHD (whose

Table 1 Frequency of response with bolus steroid induction therapy (methylprednisolone i.v. 15 mg/kg/week × 8 weeks, +prednisone 0.5 mg/kg qod) and cyclosporine

Response	*6 months, n (%)*	*1 year, n (%)*	*2 years, n (%)*
CR+PR	95 (61)	78 (53)	71 (50)
NR	60 (39)	53 (36)	64 (45)
Flare	—	17 (12)	6 (4)
NR+flare	60 (39)	70 (47)	70 (50)

Adapted from Arora *et al*.[17]

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This paper is part of a series of keynote addresses to be published in Leukemia. They were presented at the Acute Leukemia Forum San Francisco, Friday April 16, 2004
Received 12 April 2005; accepted 27 April 2005; published online 30 June 2005

Table 2 New agents in chronic GVHD

Agents	*Function*	*N*	*Complete response*	*Partial response*
Tacrolimus	Immunosuppressant	86	12 (14%)	17 (20%)
MMF	Immunosuppressant	30	6 (20%)	16 (53%)
Tacrolimus/MMF		26	2 (8%)	10 (38%)
Thalidomide	Suppression of TNF-alpha modulation of interleukins	244	47 (19%)	49 (20%)
Hydroxychloroquine	Blocks antigen presentation	32	3 (9%)	14 (44%)
Clofazimine	Immunosuppressant and antimicrobial	22	0	12 (55%)
Etretinate		27	0	20 (74%)
PUVA		40	16 (40%)	15 (38%)
ECP		110	15 (14%)	24 (22%)
Etanercept	TNF-alpha blocker	10	0	7 (70%)
Infliximab	TNF-alpha blocker	26	16 (62%)	2 (8%)
Daclizumab	Humanized anti-CD25 MoAb	4	1 (25%)	2 (50%)
Rituximab	anti-CD20 chimeric MoAb	8	0	4 (50%)

Adapted from Farag *et al* (745/id).[28]

acute disease had resolved), favorable responses were also seen, resulting in improved long-term survival. In all, 50% survive 10–15 years later.[17]

A scoring system for chronic GVHD-specific survival was developed based on the high-risk features of the extent (>50%) of skin involvement, progressive onset of chronic GVHD, and a low platelet count.[2,18] Those who had low-risk disease but still needed systemic therapy had 80% survival at 10 years, whereas those with higher risk features had only 40–50% survival at 10 years. A third of patients resolved their chronic GVHD in the first 6 months, but more than a third still had active disease beyond 2 years. At 4 years, nearly 70% of those with high-risk chronic GVHD were still being treated with immunosuppression *vs* only 30% of those with standard-risk disease.[2]

Another study examined nonrelapse mortality and survival in long-term follow-up of patients enrolled in a randomized trial comparing prednisone with or without cyclosporine for managing standard- or low-risk chronic GVHD (platelet counts >100 000/μl).[19] The authors concluded that although the addition of cyclosporine may reduce steroid-related toxicity, treatment-related mortality showed little difference over 10 years. A slight, but not statistically significant improvement in treatment-related mortality with combination therapy was observed. There was no disease-free survival improvement with combination therapy.[19] In all, 28% died while still receiving immunosuppression. Cumulative incidence of recurrent malignancy at 5 years was 39% in the cyclosporine plus prednisone arm compared with 37% in the prednisone alone arm. Survival without recurrent malignancy at 5 years was 61% in the cyclosporine plus prednisone arm compared with 71% in the prednisone arm. A statistically significant higher composite risk for transplantation-related mortality or recurrent malignancy in the cyclosporine plus prednisone arm resulted in a lower probability of survival in remission. Thus, there was no net advantage for combination chemotherapy. Standard therapy can produce control of GVHD for 50 or 60% of patients in 2–3 years, but the burden of ongoing immunosuppression is substantial.[19]

Newer therapies for chronic GVHD

Small pilot studies have suggested several new drugs as effective in managing chronic GVHD. Sirolimus plus tacrolimus was tested in a phase II study of 29 steroid-refractory patients at the MD Anderson Cancer Center. Patients received sirolimus (6 mg loading dose) with maintenance at 2 mg/day (levels 7–12 ng/ml) plus tacrolimus (levels 7–12 ng/ml). The overall response rates were 68% (18/29), with five complete responses and 13 partial responses. Response rates in the skin, mouth, eye, and GI tract were similar. Of 24 patients with skin GVHD, 8/24 (30%) had scleroderma and six (75%) responded to treatment. In patients with visceral involvement, responses were less frequent. None with lower GI tract GVHD responded.

Another sirolimus trial included 19 patients.[20] In all, 15 of 16 responded, five stopped due HUS or nephrotoxicity, and most others flared. The trial closed early.

Extracorporeal photopheresis (ECP) is another new therapy. A retrospective study of ECP was conducted in 32 patients who were beyond day 100 with steroid-dependent or steroid-refractory cutaneous chronic GVHD.[21] The study was limited to those receiving ECP for 4 weeks or more. These patients had extensive chronic GVHD and were treated an average of 36 sessions over 5 months. The total response rate was about 50%. Of seven with complete response, 5/7 had continuing complete response. Of 28 patients on systemic corticosteroid therapy at the start of ECP, 18 achieved 50% dose reduction, yielding a 64% steroid-sparing response rate. In total, 11 (34%) patients died due to visceral chronic GVHD or chronic GVHD-related infectious complications after ECP, and 66% of the patients survive, although all require continuing immunosuppression. Another report showed that ECP recipients had skin softening and improvement in liver function enzymes early in the treatment.[22] ECP is a cumbersome intervention offering similar response rates, but has some steroid-sparing potential. However, chronic GVHD-related morbidity and mortality remain high and most patients continue to require immunosuppressive therapy.

Another treatment alternative, a combination of tacrolimus plus steroids, was studied in 104 patients and suggested no major advantage to the combination.[23] These patients had a 70% response rate with 79% in the skin and 76% in the mouth, but much lower response rate in visceral disease: 41% in the GI tract and 29% in the liver. The mortality rate was 48% and chronic GVHD-specific mortality was 34%.

Other alternative agents have been used with variable outcome. The response rates for various agents are shown in Table 2. The studies were all conducted in different types of patients over varying time periods, but all patients had chronic GVHD. In most studies, the overall response rates were under

50%, suggesting only limited efficacy. For example, tacrolimus given to 86 patients in several small studies had an overall response rate of 34%. Mycophenolate mofetil (MMF) might be a potentially promising drug because the cumulative response from two studies is 73%, and it has only limited toxicity.[24,25] However, tacrolimus with MMF as salvage therapy produced a lower response of approximately 38%.[26] Prospective multicenter testing of prednisone plus or minus MMF is underway.

Thalidomide is a widely studied agent, including its use as secondary therapy for chronic GVHD,[12,27] with an overall response nearly 40% (Table 2). Two randomized trials used thalidomide for initial management of chronic GVHD. Neither study showed any response or survival advantage for thalidomide.[28]

Hydroxychloroquine has shown nearly 50% responses in a small number of patients and is being tested in an ongoing randomized trial.[29] Two other drugs, clofazimine and etretinate, yield promising partial responses and might be worthy of more study.[30,31] PUVA and ECP therapy only favorably affect skin disease, and both have variable responses.[32]

New agents reported in only a few patients include etanercept, infliximab, daclizumab, and rituximab. Etanercept showed 70% response in 10 patients,[33] infliximab had over 50% response rate,[34] and daclizumab showed a response in 3/4 patients.[35] Of note, a recently completed trial in acute GVHD showed a survival disadvantage with daclizumab, a finding that suggests caution in its future use.[36] Rituximab has been tried in three small studies; one included eight patients with some manifestations of chronic GVHD that resolved simultaneously (Cutler C *et al. Biol Blood Marrow Transplant* 2005; **11:** 10; abstract).[37,38]

Summary

From these various studies, it is apparent that the key to improving management of chronic GVHD remains elusive. Heterogeneity of patients and disease manifestations and even uncertainty in diagnosis of chronic GVHD confound all these studies. At one referral center, 15–20% of the patients referred for management of chronic GVHD were found to have no signs of the disease.[39] Treating physicians are inconsistent in recognizing the protean manifestations of this syndrome. If patients with varying symptoms are included in heterogeneous pilot studies, interpretation of their findings may be misleading. Future studies of chronic GVHD need carefully defined eligibility, consistent therapy, and clearly defined response criteria. At present, there are two prospective randomized trials underway for treatment of chronic GVHD. One is a multicenter trial for standard-risk patients comparing prednisone and cyclosporine with or without MMF. The Children's Oncology Group is comparing the addition of hydroxychloroquine to initial therapy of chronic GVHD. The outcome from these two trials will be important in offering prospective and clear data, even if the either agent is not a big advance.

An essential component of chronic GVHD medical management is ongoing supportive care over the whole length of therapy. This must include infection prophylaxis, hydration, nutrition, and careful follow-up. New strategies for abatement of chronic GVHD are essential, but more critical are new ideas to manage the immune deficiency associated with chronic GVHD, discipline in designing and executing studies, clinical caution in interpreting the outcomes, and new support systems to help patients bear the ongoing burdens accompanying this lengthy chronic illness.

References

1 Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2003; **9**: 215–233.
2 Akpek G, Lee SJ, Flowers ME, Pavletic SZ, Arora M, Lee S *et al.* Performance of a new clinical grading system for chronic graft-versus-host disease: a multicenter study. *Blood* 2003; **102**: 802–809.
3 Socie G, Stone JV, Wingard JR, Weisdorf D, Henslee-Downey PJ, Bredeson C *et al.* Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. *N Engl J Med* 1999; **341**: 14–21.
4 Lee SJ, Vogelsang G, Gilman A, Weisdorf DJ, Pavletic S, Antin JH *et al.* A survey of diagnosis, management, and grading of chronic GVHD. *Biol Blood Marrow Transplant* 2002; **8**: 32–39.
5 Sullivan KM, Shulman HM, Storb R, Weiden PL, Witherspoon RP, McDonald GB *et al.* Chronic graft-versus-host disease in 52 patients: adverse natural course and successful treatment with combination immunosuppression. *Blood* 1981; **57**: 267–276.
6 Sullivan KM, Witherspoon RP, Storb R, Deeg HJ, Dahlberg S, Sanders JE *et al.* Alternating-day cyclosporine and prednisone for treatment of high-risk chronic graft-v-host disease. *Blood* 1988; **72**: 555–561.
7 Keever-Taylor CA, Bredeson C, Loberiza FR, Casper JT, Lawton C, Rizzo D *et al.* Analysis of risk factors for the development of GVHD after T cell-depleted allogeneic BMT: effect of HLA disparity, ABO incompatibility, and method of T-cell depletion. *Biol Blood Marrow Transplant* 2001; **7**: 620–630.
8 Irschick EU, Hladik F, Niederwieser D, Nussbaumer W, Holler E, Kaminski E *et al.* Studies on the mechanism of tolerance or graft-versus-host disease in allogeneic bone marrow recipients at the level of cytotoxic T-cell precursor frequencies. *Blood* 1992; **79**: 1622–1628.
9 Ochs LA, Miller WJ, Filipovich AH, Haake RJ, McGlave PB, Blazar BR *et al.* Predictive factors for chronic graft-versus-host disease after histocompatible sibling donor bone marrow transplantation. *Bone Marrow Transplant* 1994; **13**: 455–460.
10 Kansu E, Gooley T, Flowers ME, Anasetti C, Deeg HJ, Nash RA *et al.* Administration of cyclosporine for 24 months compared with 6 months for prevention of chronic graft-versus-host disease: a prospective randomized clinical trial. *Blood* 2001; **98**: 3868–3870.
11 Storb R, Leisenring W, Anasetti C, Applebaum FR, Deeg HJ, Doney K *et al.* Methotrexate and cyclosporine for graft-vs-host disease prevention: what length of therapy with cyclosporine? *Biol Blood Marrow Transplant* 1997; **3**: 194–201.
12 Arora M, Wagner JE, Davies SM, Blazar BR, Defor T, Enright H *et al.* Randomized clinical trial of thalidomide, cyclosporine, and prednisone *vs* cyclosporine and prednisone as initial therapy for chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2001; **7**: 265–273.
13 Browne PV, Weisdorf DJ, DeFor T, Miller WJ, Davies SM, Filipovich A *et al.* Response to thalidomide therapy in refractory chronic graft-versus-host disease. *Bone Marrow Transplant* 2000; **26**: 865–869.
14 Koga Y, Nagatoshi Y, Kawano Y, Okamura J. Methotrexate *vs* cyclosporin A as a single agent for graft-versus-host disease prophylaxis in pediatric patients with hematological malignancies undergoing allogeneic bone marrow transplantation from HLA-identical siblings: a single-center analysis in Japan. *Bone Marrow Transplant* 2003; **32**: 171–176.
15 Winston DJ, Antin JH, Wolff SN, Bierer BE, Small T, Miller KB *et al.* A multicenter, randomized, double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2001; **28**: 187–196.
16 Lee SJ, Loberiza FR, Rizzo JD, Soiffer RJ, Antin JH, Weeks JC. Optimistic expectations and survival after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2003; **9**: 389–396.
17 Arora M, Burns LJ, Davies SM, MacMillan ML, DeFor TE, Miller WJ *et al.* Chronic graft-versus-host disease: a prospective cohort study. *Biol Blood Marrow Transplant* 2003; **9**: 38–45.

18 Akpek G, Zahurak ML, Piantadosi S, Margolis J, Doherty J, Davidson R *et al.* Development of a prognostic model for grading chronic graft-versus-host disease. *Blood* 2001; **97**: 1219–1226.
19 Koc S, Leisenring W, Flowers ME, Anasetti C, Deeg HJ, Nash RA *et al.* Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone *vs* prednisone alone. *Blood* 2002; **100**: 48–51.
20 Johnston LJ, Brown J, Shizura JA, Stockerl-Goldstein KE, Stuart MJ, Blume KG *et al.* Rapamycin (sirolimus) for treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2005; **11**: 47–55.
21 Apisarnthanarax N, Donato M, Korbling M, Couriel D, Gajewski J, Giralt S *et al.* Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. *Bone Marrow Transplant* 2003; **31**: 459–465.
22 Bisaccia E, Gonzalez J, Palangio M, Schwartz J, Klainer AS. Extracorporeal photochemotherapy alone or with adjuvant therapy in the treatment of cutaneous T-cell lymphoma: a 9-year retrospective study at a single institution. *J Am Acad Dermatol* 2000; **43**: 263–271.
23 De Jesus J, Ghosh S, Hsu Y, Neuman J, Cohen A, Champlin R *et al.* Tacrolimus in combination with steroids for the treatment of chronic GVHD. *Biol Bone Marrow Transplant* 2004; **10** (Suppl): 49.
24 Mohty M, de Lavallade H, Faucher C, Bilger K, Vey N, Stoppa AM *et al.* Mycophenolate mofetil and cyclosporine for graft-versus-host disease prophylaxis following reduced intensity conditioning allogeneic stem cell transplantation. *Bone Marrow Transplant* 2004; **34**: 527–530.
25 Kasper C, Sayer HG, Mugge LO, Schilling K, Scholl S, Issa MC *et al.* Combined standard graft-versus-host disease (GvHD) prophylaxis with mycophenolate mofetil (MMF) in allogeneic peripheral blood stem cell transplantation from unrelated donors. *Bone Marrow Transplant* 2004; **33**: 65–69.
26 Kim JG, Sohn SK, Kim DH, Lee NY, Suh JS, Lee KS *et al.* Different efficacy of mycophenolate mofetil as salvage treatment for acute and chronic GVHD after allogeneic stem cell transplant. *Eur J Haematol* 2004; **73**: 56–61.
27 Kulkarni S, Powles R, Sirohi B, Treleaven J, Saso R, Horton C *et al.* Thalidomide after allogeneic haematopoietic stem cell transplantation: activity in chronic but not in acute graft-versus-host disease. *Bone Marrow Transplant* 2003; **32**: 165–170.
28 Farag SS. Chronic graft-versus-host disease: where do we go from here? *Bone Marrow Transplant* 2004; **33**: 569–577.
29 Khoury H, Trinkaus K, Zhang MJ, Adkins D, Brown R, Vij R *et al.* Hydroxychloroquine for the prevention of acute graft-versus-host disease after unrelated donor transplantation. *Biol Blood Marrow Transplant* 2003; **9**: 714–721.
30 Lee SJ, Wegner SA, McGarigle CJ, Bierer BE, Antin JH. Treatment of chronic graft-versus-host disease with clofazimine. *Blood* 1997; **89**: 2298–2302.
31 Marcellus DC, Altomonte VL, Farmer ER, Horn TD, Freemer CS, Grant J *et al.* Etretinate therapy for refractory sclerodermatous chronic graft-versus-host disease. *Blood* 1999; **93**: 66–70.
32 Grundmann-Kollmann M, Martin H, Ludwig R, Klein S, Boehncke WH, Hoelzer D *et al.* Narrowband UV-B phototherapy in the treatment of cutaneous graft versus host disease. *Transplantation* 2002; **74**: 1631–1634.
33 Chiang KY, Abhyankar S, Bridges K, Godder K, Henslee-Downey JP. Recombinant human tumor necrosis factor receptor fusion protein as complementary treatment for chronic graft-versus-host disease. *Transplantation* 2002; **73**: 665–667.
34 Couriel D, Saliba R, Hicks K, Ippoliti C, de Lima M, Hosing C *et al.* Tumor necrosis factor-alpha blockade for the treatment of acute GVHD. *Blood* 2004; **104**: 649–654.
35 Przepiorka D, Kernan NA, Ippoliti C, Papadopoulos EB, Giralt S, Khouri I *et al.* Daclizumab, a humanized anti-interleukin-2 receptor alpha chain antibody, for treatment of acute graft-versus-host disease. *Blood* 2000; **95**: 83–89.
36 Lee SJ, Chakrabarti S, Walsh T, Igarashi T, Takahashi Y, Kleiner D *et al.* Improved survival in steroid-refractory acute graft versus host disease after non-myeloablative allogeneic transplantation using a daclizumab-based strategy with comprehensive infection prophylaxis. *Br J Haematol* 2004; **124**: 777–786.
37 Ratanatharathorn V, Ayash L, Reynolds C, Silver S, Reddy P, Becker M *et al.* Treatment of chronic graft-versus-host disease with anti-CD20 chimeric monoclonal antibody. *Biol Blood Marrow Transplant* 2003; **9**: 505–511.
38 Canninga-Van Dijk MR, Van Der Straaten HM, Fijnheer R, Sanders CJ, Van Den Tweel JG, Verdonck LF. Anti-CD20 monoclonal antibody treatment in 6 patients with therapy-refractory chronic graft-versus-host disease. *Blood* 2004; **104**: 2603–2606.
39 Vogelsang GB. How I treat chronic graft-versus-host disease. *Blood* 2001; **97**: 1196–1201.