414

RECOMMENDED MEASURES FOR JOINT CHRONIC GVHD: RESULTS FROM THE CHRONIC GVHD CONSORTIUM

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Assessing the degree to which chronic GVHD (cGVHD) may limit range of joint motion (ROM) needs to be accomplished reliably, simply, and in a clinically meaningful way. We evaluated NIH recommended scales and a photographic ROM (P-ROM) scale [Carpenter PA, *Blood* 2011] for their correlation with provider (MD) and patient (PT) perceptions of joint change.

Patients and Methods: As part of a multicenter, prospective, longitudinal observational cohort, 458 patients receiving systemic cGVHD therapy were studied; 177/327 (54%) with baseline P-ROM had limited ROM defined by any 1-6 P-ROM score (7 = full ROM) at the wrists, elbows, shoulders or, 1-3 score (4 = full) at the ankles. NIH cGVHD joint scoring was categorical: 0 = full ROM (or not limited by cGVHD) and scores 1 to 3 were based upon MD opinion of PT extremity tightness, degree of reduction in both ROM and activities of daily living. At follow-up visits, as anchors, PT and MD rated separately their perception of change in joint cGVHD. Multivariable models were used to measure associations between MD/PT perceived changes (improved, stable, worse) and changes in P-ROM measures, NIH joint scores, and other items in the 2005 NIH consensus recommendations.

Results: ROM limitation was common (see Table). It was seen in patients with a longer duration of cGVHD, and was associated ($p<0.01$) with NIH skin response measures, the NIH 0-3 joint score, Lee energy subscale but not the Human Activity Profile, 2-minute walk test or grip strength. Compared to previous visits with ROM limitation (N = 369 visits), both MDs (60%) and PTs (47%) were more likely to report perceived improvement than worsening (4% MD, 9% PT). In multivariable analyses, MD perceptions of change in joint cGVHD were best predicted by P-ROM wrist score ($p = 0.003$), NIH 0-3 joint score ($p<0.001$) and SF36 bodily pain subscale ($p = 0.01$). PT perceptions of changes in joint cGVHD were predicted by SF36 bodily pain score ($p = 0.01$). Changes in the extrapolated Rodnan skin score and the NIH 0-3 skin score were not associated with perceived changes in joint cGVHD by MD and PT.

Conclusions: Joint involvement is common and should be assessed in all patients with cGVHD. The NIH joint score (1 item), P-ROM scale (4 items) and the SF36 bodily pain subscale (2 items) appeared to have the most clinical utility for measuring symptom change. Finer gradations within the P-ROM's clinically relevant range (scores 4-7) may improve its sensitivity to change.

Table. Analysis of Categorical and Continuous Variables associated with ROM

Measures	ROM involved (N = 177)	ROM not involved (N = 150)	P value
Wrist P-ROM Score ("Prayer position")(%)			
7 (full)	40	100	
6	40	0	
5	11	0	
4	3	0	
3	1	0	
2	3	0	
1	2	0	
Total involved	**60**	**0**	NA*
Shoulder Abduction P-ROM Score (%)			
7 (full)	57	100	
6	27	0	
5	12	0	
4	2	0	
3	1	0	
2	0	0	
1	1	0	
Total involved	**43**	**0**	NA*
Elbow Extension P-ROM Score (%)			
7 (full)	69	100	
6	20	0	
5	8	0	
4	2	0	
3	0	0	
2	1	0	
1	0	0	
Total involved	**31**	**0**	NA*
Ankle Dorsiflexion P-ROM Score			
4 (full)	39	100	
3	54	0	
2	7	0	
1	0	0	
Total involved	**61**	**0**	NA*
NIH Skin Response Measures (%BSA), Mean (SD)			
Erythema	5.0 (15.6)	9.7 (20.1)	.009
Moveable sclerosis	4.6 (10.3)	0.8 (4.2)	<.0001
Non-moveable sclerosis	3.1 (8.8)	0.0 (0.0)	<.0001
Lee Energy Score, Median (range)	35.7 (0.0-100)	25.0 (0.0-75.0)	.002

*Comparisons for these measures are not meaningful because they are used to define joint involvement. Abbreviations: ROM, range of motion; BSA, body surface area

415

INTERRUPTION OF THE IFNγR/CXCR3 AXIS RESULTS IN ALTERED T CELL TRAFFICKING IN VIVO AND ABROGATION OF GVHD WHILE MAINTAINING A ROBUST GVL RESPONSE

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The goal of allogeneic hematopoietic stem cell transplantation (allo-HSCT) is to minimize graft-versus-host disease (GvHD) while maintaining a beneficial graft-versus-leukemia (GvL) effect. This can be achieved by infusing regulatory T cells (Tregs) which suppress GvHD but have only limited effects on GvL. Unfortunately, Tregs exist in low frequency in the peripheral blood, are costly to purify and expand, and after expansion are difficult to isolate due to the lack of cell surface markers. Thus, alternative therapeutic approaches are needed.

Using an MHC-mismatched GvHD model, B6 (H-2b) → Balb/c (H-2d), we demonstrated that infusion of IFNγR deficient (IFNγR-/-) allogeneic donor T cells induced significantly less GvHD, compared to WT T cells, as determined by survival (74% vs. 0%; $p = 0.0004$), weight loss and percentages of B220+ B cells (12.4% vs. 3.8%; $p = 0.0205$), CD3+ T cells (14.3% vs. 4.3%; $p = 0.0025$) in blood. Of note was that the IFNγR-/- donor T cells induced a robust GvL effect in both systemic leukemia and solid tumor models using luciferase-expressing A20 cells derived from Balb/c. We found that IFNγR-/- T cells responded normally to allogeneic antigens in vitro, based on mixed lymphocyte reactions, and expressed similar levels of granzyme B, compared to WT T cells. Using bioluminescence imaging (BLI) and luciferase-transduced WT and IFNγR-/- T cells, we observed that IFNγR-/- T cells trafficked primarily to the spleen while WT T cells trafficked to gastrointestinal tract and lymph nodes, which are major GvHD target organs.

These findings suggest that the reduced GvHD was not due to reduced function, altered subsets or relative deficiency of allogeneic donor T cells but from an alteration of in vivo trafficking of IFNγR-/- T cells compared to WT T cells. We further demonstrated that the IFNγR-mediated signaling in alloreactive donor T cells was required for expression of CXCR3 which has been implicated in trafficking of T cells to areas of inflammation and target organs, commonly known to be the sites of GvHD. In addition, overexpression of CXCR3 in IFNγR-/- T cells rescued the GvHD-inducing function of IFNγR-/- T cells. CXCR3-/- T cells and pharmacological approaches using inhibitors of IFNγR signaling recapitulated the anti-GvHD (and pro-GvL) effects seen in IFNγR-/- T cells after allo-HSCT. Thus, the IFNγR-CXCR3 axis represents a promising therapeutic target for future efforts to mitigate GvHD while maintaining GvL after allo-HSCT.

416

ULTRA LOW-DOSE IL-2 MEDIATED EXPANSION OF REGULATORY T CELLS AS GVHD PROPHYLAXIS FOR RECIPIENTS OF ALLOGENEIC HEMATOPOIETIC STEM CELLS

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$CD4^+$ $CD25^+$ $FoxP3^+$ regulatory T cells (T_{regs}) may prevent graft-versus-host disease (GvHD) after allogeneic hematopoietic stem cell transplantation (HSCT). We and others have previously used low-dose IL-2 therapy in HSCT recipients in an attempt to enhance antitumor immunity and observed low rates of GvHD. Retrospective analysis showed that patients who received IL-2 had higher levels of $FoxP3^+$ T cells than controls, suggesting that IL-2 may preferentially expand T_{regs} *in vivo*, thereby preventing GvHD. We therefore initiated a prospective phase II clinical trial to evaluate the efficacy and toxicity of ultra low-dose (ULD) IL-2 injections following allogeneic HSCT to promote T_{reg} expansion *in vivo* and prevent significant GvHD. As our control population, we evaluated T_{reg} reconstitution post HSCT in patients who did not receive IL-2. Twelve patients have been treated with ULD IL-2 (100,000 to 200,000 IU/m^2 3x weekly SC) post HSCT starting before day 30 and continuing for 6 to 12 weeks. Median age at time of HSCT was 14 years (range, 6y to 56y). Eight patients received matched sibling donor transplants and four received alternative donor transplants with Campath 1-H for *in vivo* T-cell depletion. By flow cytometry, all patients demonstrated a rise in the percentage of $CD4^+$ $CD25^+$ $FoxP3^+$ T_{regs} by 6 weeks following initiation of IL-2 therapy with a mean of 5.2% (range, 0 to 11.0%) pre IL-2 to a mean of 13.2% (range, 4.4 to 31.1%) post treatment. Compared to the control HSCT population, a significant rise in T_{reg} percentages was found at 1 and 3 months post HSCT in patients receiving IL-2 (1 month: 12.8% vs. 6.8%, $p = 0.008$; 3 months: 10.5% vs. 6.2%, $p = 0.02$). Functional analyses of $CD4^+$ $CD25^{bright}$ cells demonstrated suppression of mixed lymphocyte reactions. There were no grade 3 or 4 toxicities associated with ULD IL-2. No patients on study developed grade III-IV acute GvHD, compared to 4/31 (13%) of controls. IL-2 recipients also retained T cells reactive to viral and tumor antigens, and only 25% of study patients versus 61% of the control group developed viral infections. Hence, ULD IL-2 is well-tolerated, expands a $CD4^+$ $CD25^+$ $FoxP3^+$ T_{reg} population *in vivo*, and may be associated with a lower incidence of GvHD and viral infections; the study continues to evaluate these putative benefits.

417

INTERLEUKIN-15 (IL-15) ADMINISTRATION INCREASES GRAFT VERSUS LEUKEMIA ACTIVITY IN RECIPIENTS OF HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION

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The success of haploidentical (HI) hematopoietic stem cell transplantation (HSCT), suggests that graft-versus leukemia (GVL) effect might have a substantial role in this transplant modality. Rigorous T-cell depletion (TCD) of the graft decreases the occurrence of graft-versus-host disease (GVHD) in HI-HSCT, however this results in immunodeficiency and high disease relapse rate, especially in patients with resistant or residual leukemia. Therefore, enhancing GVL activity of HSCT without increasing GVHD is crucial for improving the outcome of haploidentical transplant.

Post-transplant IL-15 administration is shown to enhance immune reconstitution, particularly donor-derived NK and CD8+ T cell populations in murine models. We evaluated the efficacy of IL-15 for enhancing GVL effect in recipients of HI-HSCT. For developing clinically relevant haploidentical transplant models, different hybrid mice with B6 background that share the same haplotype (H2Kb) are used for our murine haploindentical transplant experiments. Lethally irradiated B6D2F1/J (H2Kb/d) mice are transplanted with B6CBAF1/J (H2Kb/k) TCD bone marrow (BM) and T cells at varying doses. Some animals were also given P815 tumor cells on the day of transplant. Administration of IL-15 significantly increased the numbers of CD8+ T and NK cells in the spleen and BM in the T cell depleted model at post-transplant day 28. Infusion of very low dose haploidentical T cells ($1x10^4$) with TCD-BM resulted in a conflicting effect on immune reconstitution, i.e. increased T cell numbers, and decreased NK cell population. Post-transplant IL-15 administration also changed this immune reconstitution pattern and significantly increased both T and NK cell numbers in recipients of HI-HSCT. In P815 challenged mice that were transplanted with very low dose T cell added TCD-BM, IL-15 administration significantly increased anti-tumor activity of the graft and improved survival without increasing GVHD. This effect was observed when IL-15 administration was given at a later time point rather than immediately following transplantation, possibly allowing for more donor cell engraftment and T cell proliferation to take place. IL-15 administration without T cell infusion did not result in any survival improvement. We conclude that in our experimental HI transplant models, IL-15 administration augments anti-tumor activity of the HI-HSCT without increasing GVHD risk, and this effect requires presence of donor derived T cells.

418

COMPARISON OF MYCOPHENOLATE MOFETIL (MMF) VERSUS METHOTREXATE (MTX) FOR PREVENTION OF ACUTE GRAFT-VERSUS-HOST DISEASE: RESULTS OF A META-ANALYSIS

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Background: morbidity and mortality resulting from acute and chronic GVHD remains the most serious challenge to wider applicability of T-cell replete allogeneic HCT for otherwise incurable hematologic diseases. Developing effective regimens acute GVHD (aGVHD) prophylaxis is of vital importance due to lack of effective treatments, mainly when refractory to corticosteroids. Conflicting results have been observed when comparing, directly or indirectly, MMF-based against MTX-based regimens for aGVHD prophylaxis.
Methods: a systematic and comprehensive literature search was performed using MEDLINE databases from 1966 to 07/31/2011. All completed prospective-randomized (phase II or III) clinical trials (RCT) or retrospective non-randomized comparisons (NRC) published as a full manuscript were eligible for inclusion, but data published only in abstract form was not. Outcomes extracted from selected studies (RCT = 2, retrospective NRC = 2) included: time-to-ANC engraftment, time-to-platelets engraftment, incidences of grade II-IV aGVHD and chronic GVHD (cGVHD), incidence of severe mucositis, frequency of pain control requirement, frequency of total parenteral nutrition (TPN) use, relapse rate, incidence of non-relapse mortality (NRM) and overall survival (OS).
Results: pooled analysis shows that use of MMF, for aGVHD prophylaxis, results in significantly faster platelets engraftment (pooled hazard ratio (HR) = 1.15 (95%CI, 1.08,1.23; $p<0.0001$)), a lower incidence of severe mucositis (pooled risk ratio (RR) = 0.48 (95%CI, 0.32, 0.71; $p = 0.0003$)), and less use of TPN (pooled RR = 0.52 (95%CI, 0.34, 0.80; $p = 0.003$)) or narcotics for pain control (pooled risk ratio = 0.76 (95%CI, 0.63, 0.91; $p = 0.002$)) compared to MTX.