The haploimmunostorm syndrome: A distinct clinical entity seen in HLA-mismatched cellular immunotherapy

Cohen, G.A.; Rattu, R.; Lum, L.G.; Abdels, M.; Ballen, K.K.; Dey, B.R.; Eifelsen, G.; Quessenberry, P.J.; T. Roger Williams Medical Center, Adele R. Deou Cancer Center, and The Department of Research, Providence, RI; 2. Massachusetts General Hospital, Boston, MA.

We have observed a new infusion related clinical entity named haploimmunostorm (HIS), observed after minimal immunosuppressive HLA-3/6 or 4/6 mismatched stem cell transplantation. We have performed a total of 44 HLA-mismatched transplants with escalation of the CD3 dose from 1 x 10^9 to 1 x 10^9 cells/kg using G-CSF primed PBSC, with a conditioning regimen of 100 cGy TBI. The CD34 dose was >2 x 10^9 cells/kg. This post-infusion HIS syndrome occurred in 26 out of 30 (87%) patients with a CD3 dose more than 1 x 10^9 cells/kg. In the HIS syndrome, a constellation of symptoms occurred, some with variable penetrance, in which hyperpyrexia and malaise were a constant feature occurring as early as four hours after cell infusion with a median time of 14 hours. A morbilliform rash was seen in 40% of patients. Biopsies of these rashes revealed no evidence of hyperacute or acute graft versus host disease; rather epidermal spongiosis with lymphocytic invasion was usually seen. Diarrhea was present in a smaller subpopulation of patients (20%) and biopsies taken of the colon also failed to show any evidence of acute graft versus host disease. Transient elevations of liver enzymes occurred in 40% of the patients within 6–24 hours after infusion. Hematologic manifestations consisted of marked lymphopenia, which began at the time of initial hyperpyrexia. Steroids were used successfully if the HIS syndrome lasted more than 72 hrs. Preliminary cytokine level analysis showed variable increases of serum TNF-alpha and IL-2 post bone marrow transplantation compared with pre-transplant levels. Complete cytokine level analysis is ongoing. This syndrome is believed to be immunologically based and represents neither hyperacute nor acute graft versus host disease. This syndrome is different than an engraftment syndrome reported in some patients undergoing autologous hematopoietic stem cell transplant, particularly patients with breast cancer. Engraftment syndrome occurs at the time of engraftment, opposed to HIS in which there is transient chimerism lasting on average a week after cell infusion. Engraftment syndrome is similar to HIS in that it is associated with fever and rash but deviates with presence of capillary leak and pulmonary infiltrates.

Evaluation of the structural basis of T cell allorecognition using recombinant HLA class I multimers


Graft-versus-host disease is a major complication of any stem cell transplant that uses stem cells from an HLA-mismatched donor. However, these transplants may also possess potential for cell transplant that uses stem cells from an HLA-mismatched donor. The Anthony Nolan Research Institute, Leiden, The Netherlands; 2. The Anthony Nolan Research Institute, London, United Kingdom.

We have observed a new infusion related clinical entity named haploimmunostorm (HIS), observed after minimal immunosuppressive HLA-3/6 or 4/6 mismatched stem cell transplantation. We have performed a total of 44 HLA-mismatched transplants with escalation of the CD3 dose from 1 x 10^9 to 1 x 10^9 cells/kg using G-CSF primed PBSC, with a conditioning regimen of 100 cGy TBI. The CD34 dose was >2 x 10^9 cells/kg. This post-infusion HIS syndrome occurred in 26 out of 30 (87%) patients with a CD3 dose more than 1 x 10^9 cells/kg. In the HIS syndrome, a constellation of symptoms occurred, some with variable penetrance, in which hyperpyrexia and malaise were a constant feature occurring as early as four hours after cell infusion with a median time of 14 hours. A morbilliform rash was seen in 40% of patients. Biopsies of these rashes revealed no evidence of hyperacute or acute graft versus host disease; rather epidermal spongiosis with lymphocytic invasion was usually seen. Diarrhea was present in a smaller subpopulation of patients (20%) and biopsies taken of the colon also failed to show any evidence of acute graft versus host disease. Transient elevations of liver enzymes occurred in 40% of the patients within 6–24 hours after infusion. Hematologic manifestations consisted of marked lymphopenia, which began at the time of initial hyperpyrexia. Steroids were used successfully if the HIS syndrome lasted more than 72 hrs. Preliminary cytokine level analysis showed variable increases of serum TNF-alpha and IL-2 post bone marrow transplantation compared with pre-transplant levels. Complete cytokine level analysis is ongoing. This syndrome is believed to be immunologically based and represents neither hyperacute nor acute graft versus host disease. This syndrome is different than an engraftment syndrome reported in some patients undergoing autologous hematopoietic stem cell transplant, particularly patients with breast cancer. Engraftment syndrome occurs at the time of engraftment, opposed to HIS in which there is transient chimerism lasting on average a week after cell infusion. Engraftment syndrome is similar to HIS in that it is associated with fever and rash but deviates with presence of capillary leak and pulmonary infiltrates.

Evaluation of the structural basis of T cell allorecognition using recombinant HLA class I multimers


Graft-versus-host disease is a major complication of any stem cell transplant that uses stem cells from an HLA-mismatched donor. However, these transplants may also possess potential for cell transplant that uses stem cells from an HLA-mismatched donor. The Anthony Nolan Research Institute, Leiden, The Netherlands; 2. The Anthony Nolan Research Institute, London, United Kingdom.

We have observed a new infusion related clinical entity named haploimmunostorm (HIS), observed after minimal immunosuppressive HLA-3/6 or 4/6 mismatched stem cell transplantation. We have performed a total of 44 HLA-mismatched transplants with escalation of the CD3 dose from 1 x 10^9 to 1 x 10^9 cells/kg using G-CSF primed PBSC, with a conditioning regimen of 100 cGy TBI. The CD34 dose was >2 x 10^9 cells/kg. This post-infusion HIS syndrome occurred in 26 out of 30 (87%) patients with a CD3 dose more than 1 x 10^9 cells/kg. In the HIS syndrome, a constellation of symptoms occurred, some with variable penetrance, in which hyperpyrexia and malaise were a constant feature occurring as early as four hours after cell infusion with a median time of 14 hours. A morbilliform rash was seen in 40% of patients. Biopsies of these rashes revealed no evidence of hyperacute or acute graft versus host disease; rather epidermal spongiosis with lymphocytic invasion was usually seen. Diarrhea was present in a smaller subpopulation of patients (20%) and biopsies taken of the colon also failed to show any evidence of acute graft versus host disease. Transient elevations of liver enzymes occurred in 40% of the patients within 6–24 hours after infusion. Hematologic manifestations consisted of marked lymphopenia, which began at the time of initial hyperpyrexia. Steroids were used successfully if the HIS syndrome lasted more than 72 hrs. Preliminary cytokine level analysis showed variable increases of serum TNF-alpha and IL-2 post bone marrow transplantation compared with pre-transplant levels. Complete cytokine level analysis is ongoing. This syndrome is believed to be immunologically based and represents neither hyperacute nor acute graft versus host disease. This syndrome is different than an engraftment syndrome reported in some patients undergoing autologous hematopoietic stem cell transplant, particularly patients with breast cancer. Engraftment syndrome occurs at the time of engraftment, opposed to HIS in which there is transient chimerism lasting on average a week after cell infusion. Engraftment syndrome is similar to HIS in that it is associated with fever and rash but deviates with presence of capillary leak and pulmonary infiltrates.

Evaluation of the structural basis of T cell allorecognition using recombinant HLA class I multimers


Graft-versus-host disease is a major complication of any stem cell transplant that uses stem cells from an HLA-mismatched donor. However, these transplants may also possess potential for cell transplant that uses stem cells from an HLA-mismatched donor. The Anthony Nolan Research Institute, Leiden, The Netherlands; 2. The Anthony Nolan Research Institute, London, United Kingdom.

We have observed a new infusion related clinical entity named haploimmunostorm (HIS), observed after minimal immunosuppressive HLA-3/6 or 4/6 mismatched stem cell transplantation. We have performed a total of 44 HLA-mismatched transplants with escalation of the CD3 dose from 1 x 10^9 to 1 x 10^9 cells/kg using G-CSF primed PBSC, with a conditioning regimen of 100 cGy TBI. The CD34 dose was >2 x 10^9 cells/kg. This post-infusion HIS syndrome occurred in 26 out of 30 (87%) patients with a CD3 dose more than 1 x 10^9 cells/kg. In the HIS syndrome, a constellation of symptoms occurred, some with variable penetrance, in which hyperpyrexia and malaise were a constant feature occurring as early as four hours after cell infusion with a median time of 14 hours. A morbilliform rash was seen in 40% of patients. Biopsies of these rashes revealed no evidence of hyperacute or acute graft versus host disease; rather epidermal spongiosis with lymphocytic invasion was usually seen. Diarrhea was present in a smaller subpopulation of patients (20%) and biopsies taken of the colon also failed to show any evidence of acute graft versus host disease. Transient elevations of liver enzymes occurred in 40% of the patients within 6–24 hours after infusion. Hematologic manifestations consisted of marked lymphopenia, which began at the time of initial hyperpyrexia. Steroids were used successfully if the HIS syndrome lasted more than 72 hrs. Preliminary cytokine level analysis showed variable increases of serum TNF-alpha and IL-2 post bone marrow transplantation compared with pre-transplant levels. Complete cytokine level analysis is ongoing. This syndrome is believed to be immunologically based and represents neither hyperacute nor acute graft versus host disease. This syndrome is different than an engraftment syndrome reported in some patients undergoing autologous hematopoietic stem cell transplant, particularly patients with breast cancer. Engraftment syndrome occurs at the time of engraftment, opposed to HIS in which there is transient chimerism lasting on average a week after cell infusion. Engraftment syndrome is similar to HIS in that it is associated with fever and rash but deviates with presence of capillary leak and pulmonary infiltrates.
Poster Session I

graft-versus-host reactions (GVHD) retaining a graft-versus-leukemia effect and the capability to reconstitute the immune system. CD6-depleted mbc contain a large proportion of NK and NK-T cells. 63 patients with advanced disease (AML 32, ALL 15, NHL 11, CLL 2, CML 2, SAA 1) were transplanted with marrow from family donors sharing one HLA-haplo-type and differing in 0–4 HLA-antigens of the second haplotype. Conditioning consisted of total body irradiation (TBI), antithymocyte globulin (ATG) and cyclophosphamide (CY), post-grafting immunosuppression of cyclosporin A (CSA) and a short course of methotrexate (MTX). A transfusion of donor leukocytes was given prior to CY. Complete engraftment was observed in 34 evaluable patients given 12 Gy TBI. The dose of TBI could be reduced to 4 Gy without rejection in 25 evaluable patients. GVHD was severe (grade III and IV) in 12 of 48 evaluable patients. An improved method of CD6-depletion was administered to mbc in 9 patients and severe GVHD did not develop. GVHD responded to corticosteroids in most patients. 15 patients survive disease free up to 6 years (median 784 days). Recurrent infections including PTLD were the major cause of transplant-related mortality. Absolute counts of lymphocytes, CD4 and CD8 subpopulations were not different from those of a control group of 46 patients in advanced disease given identical sibling transplants. However naive CD4 cells and TRECes were low. Rejection, GVHD and GVL have been controlled by this regimen, but immune reconstitution remains a problem that may be solved by early discontinuation of immunosuppression in this regimen.

GVH/GVL

121

ACUTE GRAFT VERSUS HOST DISEASE AFTER NON-MYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANTATION (NST) WITH LOW-DOSE TBI, FLUDARABINE AND ANTITHYMOCYTE GLOBULIN (ATG) Grosskreutz, C.L.; Scigliano, E.; Fruchtman, S.M.; Isola, L.M. Hematology-Oncology Division, Mount Sinai Medical Center, New York, NY.

Acute GVHD is a frequent complication of NST although at a lower rate and severity than after full myeloablative ATG. Given with conditioning produces substantial host immunosuppression and is thought to produce T-cell deleterious of the allograft. We previously showed that the addition of ATG to TBI 200 Gy and fludarabine can improve donor engraftment. Whether it impacts on acute and chronic GVHD and on graft versus tumor effect is less known. Forty-seven pts, not eligible for conventional allogeneic SCT, underwent NST using ATG 15 mg/kg/day (rabbit) days 4 to 5, fludarabine 30 mg/kg/day days 1-5, cyclosporin A (CSA) and a short course of methotrexate (MTX). A transfusion of donor leukocytes was given prior to CY. Complete engraftment was observed in 34 evaluable patients given 12 Gy TBI. The dose of TBI could be reduced to 4 Gy without rejection in 25 evaluable patients. GVHD was severe (grade III and IV) in 12 of 48 evaluable patients. An improved method of CD6-depletion was administered to mbc in 9 patients and severe GVHD did not develop. GVHD responded to corticosteroids in most patients. 15 patients survive disease free up to 6 years (median 784 days). Recurrent infections including PTLD were the major cause of transplant-related mortality. Absolute counts of lymphocytes, CD4 and CD8 subpopulations were not different from those of a control group of 46 patients in advanced disease given identical sibling transplants. However naive CD4 cells and TRECes were low. Rejection, GVHD and GVL have been controlled by this regimen, but immune reconstitution remains a problem that may be solved by early discontinuation of immunosuppression in this regimen.

GVH/GVL

122


In this study, we wanted to evaluate the predictive value of a sensitive chimerism method for relapse in 45 patients with acute lymphoblastic leukemia (ALL) after allogeneic stem cell transplants (SCT). The method, based on real-time PCR using single nucleotide polymorphic (SNP) markers, was shown to be more than one log more sensitive than the most common used methods. Mixed chimerism (MC) was detected in the peripheral blood (PB) and bone marrow (BM) samples of all patients that relapsed. However, a high degree of MC was also found in patients without relapse (57% MC in PB and 94% MC in BM). In some patients, still in remission, MC was found 4–5 years after SCT. In paired BM-PB samples, the level of recipient cells were more than one log higher in BM as compared to PB. Chimerism results after 3 months post-SCT were associated with relapse. In PB samples, 13/15 patients with a MC level of greater than 0.1% relapsed as compared to 3/22 patients below this level (p < 0.001). The median time between first detection of this level and relapse was 5.5 (range 0.3–4.4) months. In BM samples, 10/15 patients with a MC level greater than 1% relapsed as compared to 1/11 patients below this level (p < 0.001). The median time between first detection of this level and relapse was 18 (1.8–34) months. In conclusion, using a new sensitive chimerism method, a high incidence of MC was found after SCT. Despite this, threshold levels associated with relapse were found both in PB and BM. The time period between first detection of these levels and relapse may be long enough for immunotherapeutic interventions to have an antileukemic effect.

123

CLINICAL RELEVANCE OF RECIPIENT LEUKOCYTE INFUSION (RLI) THERAPY Saito, T.I.; Sykes, M. Transplantation Biology Research Center, Massachusetts General Hospital/Harvard Medical School, Boston, MA.

Background: Surprisingly, anti-tumor responses can occur in patients who reject donor grafts following nonmyeloablative hematopoietic cell transplantation (Dey et al., Biol Blood Marrow Transplant 7:604). In murine mixed chimeras prepared with nonmyeloablative conditioning, we previously showed that recipient leukocyte infusions (RLI) induced anti-tumor responses against host-type tumors (Rubio et al. Blood 102:2300). To further investigate the clinical relevance of this RLI model, we evaluated the effect of RLI from tumor-bearing mice and 2. compared RLI with allogeneic lymphocyte infusion in untreated mice. Methods: Mixed chimerism was achieved in BALB/c (H-2b) mice conditioned with depletion anti-CD4 and CD8 mAbs on Day 1. To further investigate the clinical relevance of this RLI model, we 1. evaluated the effect of RLI from tumor-bearing mice and 2. compared RLI with allogeneic lymphocyte infusion in untreated mice. Methods: Mixed chimerism was achieved in BALB/c (H-2b) mice conditioned with depletion anti-CD4 and CD8 mAbs on Day 1. To further investigate the clinical relevance of this RLI model, we 1. evaluated the effect of RLI from tumor-bearing mice and 2. compared RLI with allogeneic lymphocyte infusion in untreated mice. Methods: Mixed chimerism was achieved in BALB/c (H-2b) mice conditioned with depletion anti-CD4 and CD8 mAbs on Day 1. To further investigate the clinical relevance of this RLI model, we 1. evaluated the effect of RLI from tumor-bearing mice and 2. compared RLI with allogeneic lymphocyte infusion in untreated mice.

Results: In BM samples, the level of recipient cells were more than one log higher in BM as compared to PB. Chimerism results after 3 months post-SCT were associated with relapse. In PB samples, 13/15 patients with a MC level of greater than 0.1% relapsed as compared to 3/22 patients below this level (p < 0.001). The median time between first detection of this level and relapse was 5.5 (range 0.3–4.4) months. In BM samples, 10/15 patients with a MC level greater than 1% relapsed as compared to 1/11 patients below this level (p < 0.001). The median time between first detection of this level and relapse was 18 (1.8–34) months. In conclusion, using a new sensitive chimerism method, a high incidence of MC was found after SCT. Despite this, threshold levels associated with relapse were found both in PB and BM. The time period between first detection of these levels and relapse may be long enough for immunotherapeutic interventions to have an antileukemic effect.