CHRONIC GRAFT-VERSUS-HOST DISEASE AND ITS MANAGEMENT IN CHILDREN

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ABSTRACT

Chronic graft-versus-host disease is sometimes a severe, disabling and long-lasting complication of allogeneic hematopoietic stem cell transplantation. Its frequency lies between 10 and 40% of pediatric graft recipients, depending on a number of risk factors. Such factors are the type, i.e. HLA-identical related or not, gender and age of the stem cell transplant donor, original diagnosis of the patient and, most importantly, the occurrence or not of a prior acute graft-verus-host disease. Chronic graft-versus-host disease manifests itself as a collagen vascular autoimmune disease. Its treatment consists of immuno-modulatory and antiinfections drugs, in addition to supportive care and psycho-social support. Medical treatment demands a tailor-made approach and careful and prolonged surveillance.

Key words: haematopoietic stem cell transplantation, chronic graft-versus-host disease, children.

INTRODUCTION

Chronic graft-versus-host disease (GVHD) is a possible complication of allogeneic hematopoietic stem cell transplantation (HSCT), starting mostly between 50 and 150 days after HSCT and frequently running a severe and protracted course. Its appearance may either be contiguous to acute GVHD (progressive form), after an interruption following acute GVHD (quiescent form), or *de novo*, i.e. without prior acute GVHD. The severity of chronic GVHD is graded according to clinical, laboratory and histologic criteria as limited or extensive [1]. The disability accompanying chronic GVHD may be scored according to the Karnofsky (adults) or Lansky (children) performance scale. The course on treatment may be improving, stable or progressive leading to death of the graft recipient in 25 to 45% of the cases [2,3].

Chronic GVHD is an alloimmune disease with a phenotype resembling one of the collagen vascular (autoimmune) diseases. It is triggered by differences in major and minor histocompatibility antigens between the donor and the recipient, and it is effectuated by T-lymphocytes of the donor. The spectrum of pathological lesions is comparable to that seen in the experimental parent into F1 (non-irradiated) mouse model, with a major histocompatibility antigen difference [4]. In minor histocompatibility antigen mismatched (lethaly irradiated) mouse models it can be seen that low numbers of donor T-lymphocytes still may produce chronic GVHD, whereas acute GVHD can largely be reduced by decreasing the number of T-lymphocytes in the graft [5]. Factors which may influence the severity of chronic GVHD are the number of mature T-lymphocytes in the graft, as illustrated by a significantly increased risk of chronic GVHD after peripheral blood stem cell transplantation (PBSCT) as compared with bone marrow transplantation (BMT) [6], and the occurrence of late infections after HSCT, e.g. CMV and VZV infections [7]. Furthermore, there are indications that chronic

GVHD may in part be due to a failure in inducing tolerance to (auto) antigens or to a relative lack of regulatory T-lymphocytes, as a result of damage to the thymus, e.g. by the conditioning, by CSA or by acute GVHD [8,9]. Whether recipient cytokine polymorphism, e.g. for IL-6, is associated with the development of chronic GVHD [10] still needs further investigation.

CLINICAL PRESENTATION AND PATHOLOGY

Chronic GVHD manifests itself as a collagen vascular disease with a wide spectrum of tissue abnormalities [11,12]. Hyper- and hypopigmentation can be seen in the skin, and its texture can become scleroderma-like, sometimes resulting in contractures of major joints which may lead to severe invalidity. In cases where the scalp is affected hair loss frequently ensues. Mucous membranes, especially of the eyes and the oral cavity are frequently involved in the process, resulting in the so-called sicca syndrome or Sjögren's syndrome. It frequently starts with white striae on the mucosa of the cheeks, lips and palate resembling lichen planus; the lesions may progress towards ulcers which are painful. Damage to the salivary glands results in dryness of the mouth. Eye involvement is a kerato-conjunctivitis sicca, with a reduction in tear formation and complaints of grittiness and discomfort. Involvement of the mucous membranes of the esophagus and intestinal tract is infrequent, and especially the latter must be regarded as a consequence of scar formation following acute GVHD of the gut. Different other organs may take part in the process, albeit less frequently. Chronic GVHD of the liver becomes cholangiolitis and manifests itself as obstructive jaundice and may finally result in vanishing of small bile ducts. Obliterative bronchiolitis is rare and manifests itself as an obstructive lung disease, with dyspnoea and wheezing. It is often fatal because its diagnosis may be delayed due to its slowly progressive character. Also polymyositis, fasciitis and serositis may occur. Sometimes complications are indistinguishable from idiopathic autoimmune diseases and may be associated with mononuclear inflammatory lesions or the deposition of antibodies in tissues such as muscles and kidneys. Also autoimmune haemolytic anaemia and thrombocytopenia may be found. Lymphoid tissue, e.g. the spleen, may become hypocellular and atrophic, which explains the predisposition for infections with, e.g. pneumococci.

When chronic GVHD progresses, the immune dysfunction also progresses, which leads to recurrent infections, e.g. with pneumoccoci and other bacteria, yeasts and molds, and viruses such as VZV [11]. The increased risk of severe infections is the result of both the lesions of the skin and mucous membranes and the hypotrophy of lymphoid tissue, and of the continued administration of immunosuppressive drugs to treat chronic GVHD. The most frequent cause of death in case of treatment failure are additional infections.

Histopathology does not provide much information. The findings confirm what may be expected from the clinical abnormalities. Only in cases of diagnostic doubt or when a change in treatment is considered, histological examination may give relevant additional information, e.g. with respect to the activity of the inflammation or severity of tissue damage such as in the case of progressive liver or kidney failure.

RISK FACTORS

There have been performed some large retrospective studies, using life-table analysis to study the possible relationship of several tens of variables for their association with chronic GVHD: one IBMTR (International Bone Marrow Transplant Registry)-study analyzed the data of 2534 evaluable BMT-recipients, grafted between 1982 and 1987 [13], another analyzed the data of a single center (Huddinge, Sweden) encompassing 451 evaluable BMT-recipients, grafted between 1975 and 1996 [14]. Univariate analysis of risk factors revealed a restricted number of factors significantly associated with chronic GVHD. Prior acute GVHD, increasing recipient age (or reci-

pient age greater than 20 years), use of non-TCD bone marrow (for HLA-identical sibling transplants) and alloimmune female donors for male recipients were found in the IBMTR study [13],whereas prior acute GVHD, increasing recipient age, alloimmune female donors for male recipients and chronic myelogenous leukemia (CML) compared with other diagnoses were revealed in the Huddinge study [14]. Thus the pattern of major risk factors showed great resemblance.

At the Leiden Pediatrics BMT-Center we were able to study 407 evaluable transplants performed between the end of 1968 and 2001. These were all consecutive graft recipients, who survived for more than 50 days following transplantation, and who had an engraftment of donor cells. Two hundred and seventy three children received an HLA-identical sibling donor transplant (IRD) and 134 either a haplo-identical related donor (ORD) or matched unrelated donor (MUD) transplant. The mean incidence of chronic GVHD was 12.8% (52 out of 407), of which 23 were limited and 29 extensive. Patient and transplant characteristics, and the frequency of chronic GVHD are given in *Tab. 1.*

Information obtained from the EBMT (European Group for Blood and Marrow Transplantation)-registry Working Parties indicated that for patients aged under 16, the mean frequency of chronic GVHD following HLA-identical sibling BMT, was 17% in patients with AML-1st CR, 20% in patients with ALL-2nd CR, 26% for patients with SAA, and 37% for patients with adult-type CML. The Leiden Pediatrics population was analyzed with regard to the contribution of different possibly relevant discontinuous variables for chronic GVHD, using Pearson's chi-square test with Yates' correction. The following variables were found to significantly increase the risk of chronic GVHD: prior acute GVHD, donor age (donors below the age of 5 years gave significantly less chronic GVHD), type of donor (HLA-identical related donors (IRD) gave significantly less chronic GVHD than haplo-identical related donors (ORD) or matched unrealted donors (MUD)), diagnosis (significantly less chronic GVHD in acute leukemia patients than in other diagnoses) and GVHD profylaxis (i.e. CSA + MTX resulted in less chronic GVHD than either of the drugs given alone). That we could not find an increased risk for chronic GVHD

Tab. 1. Diagnosis, transplant characteristics and chronic GVHD of the Leiden Pediatrics patients.

Diagnosis	nrs	IRD (cgvhd)	MUD (cgvhd)	ORD (cgvhd)	cGVHD (%)
SAA and BM-hypoplasia	83	64 (10)	10 (3)	9 (0)	13 (16%)
SCID and other ID	50	14 (1)	15 (4)	21 (8)	13 (26%)
AML, ALL, NHL,	195	157 (12)	25 (0)	13 (2)	14 (7%)
MDS, CML	67	31 (3)	29 (6)	7 (2)	11 (16%)
Inborn errors	12	7 (0)	5 (1)	0	1 (8%)
Total	407	273 (26)	84 (14)	50 (12)	52 (13%)

IRD: HLA-identical related donor, MUD: matched unrelated donor, ORD: other (e.g. haplo-identical) related donor
SAA: severe aplastic anaemia, (SC) ID: (severe combined) immunodeficiency, AML: acute myelogenous leukaemia, ALL: acute lymphoblastic leukaemia, NHL: non-Hodgkin lymphoma, MDS: myelodysplastic syndrome, CML: (adult-type) chronic myelogenous leukaemia

following transplantation with "alloimmune" female donors may be due to the fact that 243 (60%) of the donors were aged under 16.

MANAGEMENT AND OUTCOME

Chronic GVHD demands a carefully monitored and prolonged treatment, including a multidisciplinary approach. The mainstay consists of immunomodulatory treatment and antimicrobial profylaxis or treatment, if indicated. It is important to start with a careful initial evaluation of all tissues that may be affected, so as to have a starting point for the assessment of response to therapy or progression of the disease. It goes beyond the scope of this contribution to give detailed information how to proceed in individual cases; only general lines of action can be provided. For detailed information the reader is referred to the paper of Georgia Vogelsang [15]. The baseline immunomodulatory treatment consists of continuation of CSA, addition of corticosteroids (medium dose, i.e. equivalent to 2 mg/kg/day prednisolon) and also of azathioprine especially when the course is stable or slowly improving. Preferably an alternate day corticosteroid treatment schedule should be instituted after a few weeks. It is our policy to switch to alternative therapy when the process has not stabilized after some 4 weeks, or is flaring up. The alternative approach is tailormade and depends on the type of tissues involved. Possible approaches are extracorporeal photophoresis [16], psoralens plus ultra violet light (PUVA) [17], mycophenolate mofetil (MMF) [18] or thalidomide [19]. Some of these treatment modalities have a steroid-sparing effect. In case of flaring up of GVHD, a course of anti-CD25 monoclonal antibody may suppress the reactivation.

Besides the use of immunomodulatory drugs, also antimicrobials are indicated because of the increased susceptibility to infections of the patient with chronic GVHD. It is advisable to continue antimicrobial profylaxis with trimethoprim-sulfamethoxazol, penicillin-V (pneumococci) and intraconazol oral solution (molds), as long as immunosuppressive drugs are given or even better, as long as the immune capacity of the patient is compromised. If indicated, i.e. in the case of decreased serum levels of IgG and lack of reaction to test-vaccinations, support with immunoglobulins parenteraly may be necessary. Re-vaccination with the usual set of vaccines (not with life-attenuated vaccines for some years after BMT) should be considered.

It seems possible to segregate patients into prognostic categories once chronic GVHD has become manifest and standard treatment has been started. The group of Vogelsang developed such a prognostic model and discerned some four variables which increased the risk of a progressive course c.q. a fatal outcome [3]. These variables were an extensive skin involvement (> 50% of body surface area), a persistent thrombocytopaenia (<100.000/ μl), a progressive form of chronic GVHD and a Karnofsky performance score of less than 50. Such a prognostic model may allow the identification of patients needing alternative treatment. The outcome of 52 patients with chronic GVHD, treated at Leiden Pediatrics, is shown in *Tab. 2*. Fifteen patients died as a consequence of chronic GVHD or its treatment, 9 due to infection, 2 as a result of progressive pulmonary insufficiency, 2 due to multi-organ failure, 1 due to bronchiolitis obliterans and 1 as a result of progressive renal failure (chronic nephritis following haemolytic uremic syndrome).

Tab. 2. Outcome of children with chronic GVHD at Leiden Pediatrics according to treatment.

Treatment	nrs	improved	stable	progressed	died
no or local	4	3	1	0	1
cortic +/- CSA	30	21	4	5	8
cortic + aza +/- CSA	7	3	1	3	3
"tailor-made"	11	6	2	3	3
Total	52	33	8	11	15

cortic: corticosteroids, CSA: cyclosporin A, aza: azathioprine

CONCLUSIONS

Chronic GVHD is a severe, frequently disabling and protracted complication of allogeneic HSCT. Its clinical manifestation is comparable to that of collagen vascular autoimmune diseases. Some of the major risk factors for its onset are either irrelevant in the pediatric setting, i.e. a recipient age of above 20 years, or may be circumvented, e.g. the gender of the donor and the prevention of acute GVHD; others can not be circumvented e.g. the original diagnosis and the need to use another donor than an HLA-identical sibling. It is important to assess the severity of chronic GVHD, once present, as precisely as possible in order to provide the most appropriate therapy. A multidisciplinary approach using taylor-made treatment, and a careful evaluation of its result in studies including a great number of cases seem indicated.

ACKNOWLEDGMENT

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