Key Note and State of the Art Lectures

Autologous or Allogeneic Hematopoietic Cell Transplantation For Non-Hodgkin's Lymphoma?

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Introduction

Non-Hodgkin's lymphoma (NHL) is a hematologic malignancy for which a rather dramatic rise in incidence has been noted during the past decade. NHL is a heterogeneous condition in every respect. There is a wide range of histologic, immunologic, molecular and clinical expression of this condition with marked differences in response to therapy and survival. Various forms of combination chemotherapy and radiation have been proven to be successful for the different types of NHL, however, on average only one-half of the patient population with disseminated disease enters a durable remission [1].

During the past 25 years, many investigators have explored various forms of high dose therapy followed by either autologous or allogeneic hematopoietic cell transplantation. This review will present some of the original data and provide new information from more recently published clinical trials.

Autologous Hematopoietic Cell Transplantation

The first group of patients treated with high dose combination therapy followed by autologous HCT dates back to 1978. In a report from the National Cancer Institute, 12 NHL patients were described of whom four currently are alive and well more than 25 years after HCT [2]. This encouraging observation was followed by a large number of clinical trials, mostly designed as feasibility trials or phase II studies. A comparison between high dose therapy and autologous HCT *versus* standard dose chemotherapy was reported in 1995 and demonstrated a significant advantage with respect to overall survival and disease-free survival in favor of transplantation [3].

During the past decade, patients with NHL who had high risk features have been transplanted electively during their first clinical remission in order to avoid an early relapse. These extended phase II trials have yielded promising results. A prospective comparison showing the advantage of high dose sequential therapy *versus* continued standard dose therapy was reported five years ago [4].

The leading cause for treatment failure after autologous HCT for NHL is the relapse of the underlying disease. A number of strategies to improve the outcome of autologous HCT can be pursued (see Table 1). In this presentation, I will show several examples which indicate the importance of some of the treatment strategies mentioned in Table 1 [5].

Table 1. Opportunities to Improve the Outcome of Autologous Hematopoietic Cell Transplantation

• Timing of autologous HCT with respect to remission status
• Selection of myeloablative doses and combinations of drugs with or without irradiation
• Optimizing the graft, i.e., removal of clonogenic tumors without loss of activity for hematopoietic reconstitution
• Post-autologous HCT to consolidate remission (cytokines, monoclonal antibodies, vaccines, cells, involved-field radiation)

The timing of high dose therapy and autologous HCT can have a major influence upon the treatment result. In a prospective phase II trial, we treated 37 patients with high dose therapy and autologous bone marrow transplantation for follicular lymphoma in first complete or partial remission [6]. Seventeen patients were in first complete remission and 20 patients were in partial remission. The median age of this patient population was 37 years ranging from 24 to 49 years. The preparatory regimen consisted of fractionated total body irradiation (1,200 cGy), etoposide (60 mg/kg) and cyclophosphamide (100 mg/kg). All patients received autologous bone marrow cells which were purged with a set of monoclonal antibodies directed against CD9, CD10, CD19 and CD20 with complement lysis. An intent-to-treat analysis is shown in Figure 1.

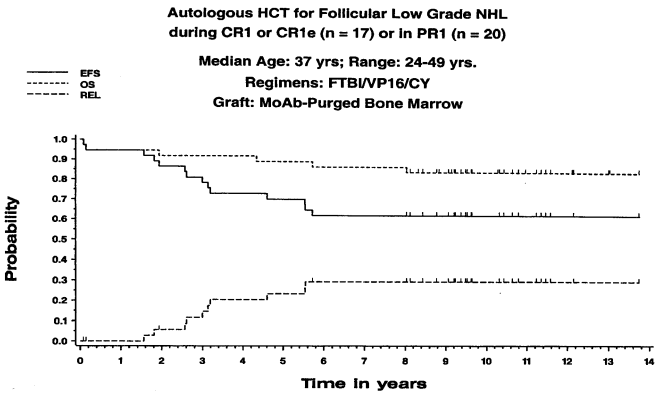

Figure 1: Overall survival, event-free survival and relapse following autologous bone marrow transplantation in 37 patients with follicular lymphoma during their first complete or first partial chemotherapy-induced remissions

At the time of analysis, the 31 surviving patients had been followed for 8–14 years. Overall survival was 84%, event-free survival 62% and the relapse rate was 29%. The causes for treatment failure included one early death due to septicemia, two patients died from acute leukemia and three patients succumbed to lymphoma. The excellent long-term survival demonstrated in this study indicates that the natural course of the underlying disease has been markedly altered by the autologous HCT approach. A case-matched comparison from the Stanford NHL data base indicates a significant survival advantage compared to patients not undergoing transplantation.

Conversely, patients with follicular lymphoma who proceed to transplantation have a reduced chance for long-term survival. Four groups of investigators at Boston, London, Omaha and Stanford have evaluated 360 autologous HCT recipients in four independent trials. Four to eight years following autologous HCT, overall survival ranged from 60–69% and freedom from relapse ranged from 42–63%. The event of a relapse of follicular NHL clearly reduces the chance for disease-free survival.

A prospective clinical trial in follicular lymphoma has been completed recently in Europe. In this study, patients with this type of lymphoma were treated with cytoreductive therapy to minimal disease and were then randomized to receive either high dose radiochemotherapy and autologous HCT or interferon. The data of this trial are currently being prepared for publication. A preliminary review indicates a statistical advantage in progression-free survival in favor of transplantation (W. Hiddemann, personal communication, 2002).

Other efforts to overcome the relapse problem include the use of maximum tolerated regimens with or without total body irradiation. More recently, radiolabeled monoclonal antibodies have been introduced and these interesting efforts have yielded promising results [7].

Another approach to reduce the post-transplant relapse rate is the employment of monoclonal antibodies directed against epitopes expressed on lymphoma cells. In an exploratory trial, we have administered the antibody directed against the CD20 epitope to 35 autologous HCT recipients whose lymphoma cells expressed CD20 [8]. These 35 patients had a median age of 51 years ranging from 28 to 70 years. Following our standardized transplant approach, an intent-to-treat analysis shows that 31 of 35 patients are alive and 29 are in continued complete remission with a follow-up period ranging from 1.3 to 4.1 years. A comparison with similar autologous HCT recipients with NHL who had not been treated with the monoclonal antibody after transplantation indicates that

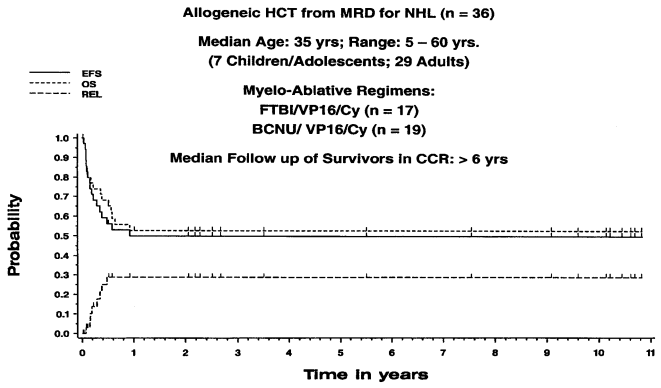

Figure 2: Overall survival, event-free survival and relapse of 36 patients who were treated with a myeloablative regimen followed by allogeneic HCT from matched related donors (MRD) for NHL

this new post-transplant therapy has contributed positively to the treatment outcome. Clearly, a prospective randomized study is needed to confirm our promising observation. Such a trial is being performed under the auspices of the Eastern Oncology Group (ECOG Trial 2199).

Allogeneic Hematopoietic Cell Transplantation

In 1986, a first group of 17 patients (14 with NHL and three with Hodgkin's disease) was described indicating that extended disease-free long-term survival can be attained with high dose therapy followed by allogeneic transplantation utilizing hematopoietic cells obtained either from fully or closely matched related donors [9]. The treatment outcome was greatly influenced by the remission status of the transplant recipient at the time when preparation for transplantation was begun, age of the recipient, compatibility with the respective donor and incidence of post-transplant complications. The leading cause for treatment failure remains graft-versus-host disease (GVHD) with associated infectious complications, other toxicities or relapse of the underlying disease. Figure 2 illustrates our institutional experience with 36 patients (seven children/adolescents and 29 adults). The median age of the patient population was 35 years ranging from 5 to 60 years. Median follow-up in continued complete remission of survivors is in excess of six years ranging from six months to more than 10 years. Overall survival is 50% with relapse causing treatment failure in 30% of allogeneic HCT recipients. The remaining 20% of patients succumbed to complications such as graft-versus-host disease, infections or veno-occlusive disease. This limited experience is nevertheless representative for the observations made in other trials including results reported from the International Bone Marrow Transplant Registry. Without question, non-relapse mortality (mostly due to GVHD) is a major obstacle to success and alternative technologies need to be explored.

Very promising data have recently been reported related to the use of intensity-reduced regimens followed by allogeneic HCT [10]. It can be expected that this novel concept which relies mainly on a graft-versus-lymphoma effect will lead to an increase in the successful use of allogeneic HCT while the procedure-related mortality is dramatically decreased as compared to high dose therapy regimens.

Conclusion

The transplant physician who evaluates and counsels a patient with NHL concerning the type of transplantation is faced with a serious dilemma. Because of the heterogeneity of the underlying disease, it has so far not been possible to come to a clear recommendation which of the types of HCT should be pursued for any given patient, autologous or allogeneic HCT. The earliest comparison was reported 15 years ago and indicated equivalence in outcome [11]. Since then, another 10 comparative studies have been described in the peer reviewed literature. In these trials, 1,183 allograft recipients were compared to 10,087 autograft recipients [12]. Differences in histology, remission status, source of autologous or allogeneic cells (marrow *versus* peripheral blood, related *versus* unrelated donor) and post-transplant management make even a meta-analysis relatively meaningless. One can only conclude that autologous HCT is associated with a post-transplant relapse rate in the order of 40–50% while allogeneic HCT is complicated mostly by GVHD and related toxicities resulting in equivalent outcomes for patients with NHL.

A collaborative trial is currently planned by the Bone Marrow Transplant Clinical Trials Network in the United States to address this important question which should help to facilitate the proper choice for transplant candidates. For the time being, most centers would utilize HCT if a suitably matched donor is available and to offer autologous HCT in the absence of a compatible donor.

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Non-Infectious Lung Complications after Transplantation

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Introduction

Mortality after hematopoietic stem cell transplantation (HSCT) could be reduced to approximately 10% in HLA-identical intrafamiliary pediatric transplantations and ranges between 20 and 40% in HLA-different, intrafamiliary as well as HLA-unrelated transplantations. In contrast, pulmonary complications are a leading cause of mortality after HSCT and contribute markedly to the morbidity [33]. The pathophysiology of these diseases is poorly understood and their classification is highly descriptive. This overview is focussed on the pediatric age group and (1) elucidates the circumstances which render recipients at increased risk of non-infectious pulmonary complications, (2) describes the diseases and alterations which are encountered, and (3) discusses diagnostic and therapeutic consequences.

General Considerations

Incidence and Prevalence

The number of hematopoetic stem cell transplantations has increased in recent years [53]. Statistically, pulmonary complications with respiratory insufficiency account for as much as 60% of the mortality, depending on the patients' age [12, 19, 36, 70, 64]. Furthermore, respiratory insufficiency is included under diagnoses such as graft-versus-host-disease (GVHD) or multi organ insufficiency. The largest retrospective analysis of Italian children after allogeneic stem cell transplantation demonstrated a pulmonary mortality of 9% [28]. Case reports as well as retrospective or prospective analyses of different patient cohorts demonstrate between 10% and 40% incidence of irreversible pulmonary function loss after HSCT [68, 14, 48, 65, 43, 11]. The incidence of late-onset non infectious pulmonary complications (LONIPC) is estimated to be approximately 10%. In one study 18 out of 179 patients suffered such complications three months after allogeneic HSCT [60, 10]. There has been no improvement over the past decade (11).

Risk Factors

Risk factors are intrinsic to the procedure (autologous vs. allogeneic transplantation with rejection by residual host T-cells, GVHD), to the immunosuppression (total body irradiation, cyclophosphamide and busulfan, both leading to interstitial pulmonary fibrosis), to the underlying disease (sickle-cell anemia with recurrent episodes of chest syndrome and pulmonary infarction, severe combined immunodeficiency with recurrent episodes of pneumonia), to the treatment of the underlying disease (irradiation, resection) and the hyperimmune status (influenced by the histocompatibility between donor and host, e.g. donor T-cells reacting to HLA-antigens). In one series of children undergoing transplantation for hematologic diseases, 44% had pulmonary function abnormalities before the procedure (11). Although the topic of this review is non-infectious pulmonary complications, it is impossible to completely distinguish these from infectious ones, as the latter may trigger hyperimmune reactions, lead to vascular alterations, enhance antigen presentation and fibroblast activity, attract neutrophils and eosinophils with release of their toxic products and disturb the level of immunotolerance. In contrast, augmented immunosuppression in the course of interstitial lung disease enhances the susceptibility for infections leading to additional damage. The extent of pulmonary mortality and morbidity, the degree and the spectrum of pulmonary diseases in children as well as the relevance of possible monocausal or multifactorial etiologic risk factors (GVH-disease, irradiation, chemotherapy especially with cyclophosphamide, bleomycin, busulfane, melphalane) is still classified insufficiently [26, 52, 8, 17, 3]. The introduction of fractional irradiation schedules has led to a reduction of the incidence of interstitial pneumonia [17]. Latent viral infections, GVHD and cytotoxic factors are not well defined in their pathogenetic role and

data about the influence of fungi is limited [5, 20, 13]. Histologic evaluations of lung tissue in GVHD-patients show epithelial and interstitial lesions typical for GVHD of the skin and the intestine [83]. There is some evidence for an active role of CMV in bronchiolitis obliterans (BO) as well as in interstitial pneumonias. Since the detection of CMV in bronchoalveolar lavage (BAL) can be taken as an indicator of invasive infection [9, 69, 63], screening for CMV in BAL and blood has been suggested as a basis for rigorous treatment [38, 1, 30, 39, 25]. The same may hold true for other viruses such as adeno-, EBV, influenza, parainfluenza virus, HHV-6 and RSV (75, 34).

Time Course of Complications

It is usual to separate pulmonary complications up to day 100 (early) from those after day 100 (late), although for some risks the division is arbitrary. If one follows lung function parameters over time in clinically asyptomatic patients after HSCT for childhood leukemia [11], abnormalities can be observed in more than 80% of patients with predominance of a restrictive pattern 6 months after transplantation (possibly due to conditioning). Lung function abnormalities tend to persist in patients with advanced disease states before transplantation but decrease by 50% in those with transplantation at early stages of childhood leukemia, suggesting a summation of adverse effects. Toxic pulmonary reactions may occur within 90 days after irradiation. Clinically overt non-infectious pulmonary complications in the neutropenic (early) phase after transplantation occur in the form of engraftment-syndrome, idiopathic pneumonia syndrome (IPS) or diffuse alveolar hemorrhage-syndrome (DAH). Furthermore the lung can be part of a systemic vascular process (capillary-leak-syndrome, thrombotic-thrombocytopenic purpura or cytokine-syndrome). Late pulmonary sequelae manifest as bronchiolitis obliterans (BO), bronchiolitis obliterans organizing pneumonia (BOOP) or fibrosis.

Cells and Structures, Immune Mechanisms

There are several distinct cellular systems involved in the maintenance of pulmonary integrity and, accordingly, in the disease process: (a) Alveolar cells or pneumocytes are a source of surfactant and contribute to metabolism within the lung as well as to lung defence. (b) Bronchial epithelial cells contribute to the clearance of bacteria and are important barriers against invasion. (c) Vascular endothelial cells are essential for regulating gas exchange, fluid homeostasis (selectins, endothelin), and the migration of blood cells. (d) Fibroblasts are sources of metalloproteinases and contribute to the repair (and fibrotic changes) of lung tissue. (e) Dendritic cells act as antigen-presenting-cells. (f) T-cells target pulmonary structures in GVHD or autoimmunity. (g) Neutrophils are the leading cells in bacterial defense but are also sources of proteases with strong elastolytic activity. (h) Recently a role has been proposed for alveolar macrophages in disease processes after HSCT (76). It is beyond the scope of this review to evalute the literature on the spectrum of immune mechanisms which include direct and indirect allorecognition as well as the activation of chemokines and lymphokines.

Diagnostic Procedures

Pulmonary diagnostics include lung function testing (bedside with portable spirometers, bodyplethysmography), capillary blood gas analysis, non-invasive transcutaneous assessment of oxygen saturation, exercise tests, bronchoalveolar lavage (BAL), transbronchial (TBB) or open lung biopsy, ultrafast or thin section computed tomography (CT) (45, 49, 27, 21, 50, 19, 54). Material obtained should be evaluated by the most sensitive and specific microbiological and pathological techniques (7).

Differential Diagnoses

In the early phase, infectious complications are the leading differential diagnoses, predominantly by gram-positive and gram-negative bacteria of the endogenous flora. In prolonged neutropenia, invasive fungal infections pose considerable diagnostic and therapeutic problems. Secondly, infections by cytomegaly, EBV, adeno-, respiratory-syncytial, parainfluenza and influenza virus, HHV-6, as well as by chlamydia, mycoplasms, legionella, mycobacteria, toxoplasma, and pneumocystis-carinii should be considered. Infections by herpes virus have reached their nadir 90 days post HSCT. However, all viral, bacterial and fungal infections can also occur at a later time point depending on the state of immunity, donor selection, and preparation of the transplant. Furthermore, GVHD and its therapy play a pathogenetic role in the development of so-called non-infectious pulmonary complications. The treatment or prophylaxis of infectious diseases may have equally profound impact on the pattern of non-infectious lung diseases observed (4).

Selected Diseases

Idiopathic Pneumonia Syndrome

Among non-infectious pulmonary complications in the early phase, a group of diffuse interstitial pneumonias is responsible for high mortality. Some of these alterations were defined at the 1991 NIHLBI Workshop in Bethesda as “idiopathic pneumonia syndrome” (IPS) [15]. Immediately after transplantation the so-called “engraftment syndrome” or “capillary-leak syndrome” play an important role (47), which has to be distiguished from diffuse alveolar damage (DAD) or the idiopathic pneumonia syndrome. The latter ones are considered primarily as forms of ARDS because their time course, their histopathologic morphological criteria and their clinical appearance closely resemble this complication – which, despite various causes, generally has an unfavourable prognosis [12, 13]. The incidence of IPS after allogeneic HSCT has been reported as 12% [15] or 8% [41] for all ages, and is certainly lower for all donors among children. The mortality of this complication is high, despite intensive care treatment including mechanical ventilation (36). According to a retrospective analysis of 1165 HSCT patients, mortality is estimated to be around 70% [41]. Essential diagnostic criteria are (1) indicators of diffuse alveolar damage (multilobular infiltrates in thorax X-ray or disturbance of gas transfer, a restrictive ventilatory defect, clinical signs of pneumonia) and (2) the exclusion of active infection of lower airways by bronchoalveolar lavage (BAL) or transbronchial biopsy (TBB). Patients with severe acute graft versus host disease (GVHD grade III-IV) have a largely increased risk of developing IPS. It has not been clear whether IPS after transplantation represents T-cell-mediated lung damage (e.g. “acute GVHD of the lung”) or is triggered by occult viral infections (e.g. adeno or HHV-6), or can be considered as a consequence of a multiple organ failure during generalised activation of inflammatory mediators (analogous to the multifactorial ARDS of non-transplanted patients) in acute GVHD, in the course of viral infections or sepsis. There is no specific therapy for the IPS to date. Therefore diffuse infiltrates on X-ray after transplantation have to be subject to a thorough work-up. If they do not respond to diuretics (to exclude pulmonary edema), they have to be evaluated radialogically, treated empirically for a short time and/or evaluated invasively depending upon the radiological appearance before or shortly after the start of antibiotics. Diagnostic criteria for “capillary leak syndrome”, which also occurs in the early phase after transplantation, are inadequate weight gain and disturbance of gas transfer. Therapy with C1-esterase inhibitor is currently under evaluation (56).

Diffuse Alveolar Hemorrhage Syndrome

Diffuse alveolar hemorrhage syndrome (DAH) is another early “non-infectious” pulmonary complication (day +7 until +40). Its occurrence has been described predominantly after autologous transplantation [78, 2]. Mortality of this disorder ranges from 50–80%. Nonspecific symptoms such as progredient dyspnoea, dry cough, fever, hypoxia and diffuse lobular consolidation in X-ray are considered typical. Hemoptoe is rare. Early diagnosis (BAL) is important since high-dose corticosteroids can then be applied efficiently [70].

Bronchiolitis Obliterans

Because of its high mortality, the late complication “bronchiolitis obliterans” (BO) stands – together with non-classifiable interstitial pneumonia, – in the first line of differential diagnoses for non-infectious pulmonary complications after HSCT. Not unlike BO after lung transplantation, the etiology remains unclear. Lymphocyt-

ic bronchitis, alloreactivity after pathologic expression of antigens due to stress (viral, radiation, medications), malnutrition of the bronchial wall, vascular changes, occult aspirations – are all considered to be causative events (71). Histologically the disease resembles BO in patients after heart-lung and lung transplantation; it is interpreted as chronic rejection (prevalence >35%) with high mortality (25%) [79]. The first description of BO after allogeneic hematopoetic stem cell transplantation dates from 1982 [66]. Since then this complication has been described after all types of transplantation, including cord blood cell transplantation [57]. In adults one assumes a prevalence of bronchiolitis obliterans after hematopoetic stem cell transplantation in a range between 5–10% [62, 81]. In children, incidences of up to 20% have been reported [68]. If unrecognised, this late complication tends to be lethal, since the therapeutic effect of corticosteroids in advanced stages is poor. The speed of progression for BO and the ideal time for therapeutic intervention are unknown. BO is frequently associated with chronic GVHD [81, 60] and they occur in combination in up to 10% of adult patients [42] and up to 30% in children with GVHD [68]. The clinical symptoms are nonspecific with expiratory wheeze, cough, dyspnoea and hypoxia upon exertion. Typical HR-CT-signs of the thorax for BO are peripheral hypovascularity, enlargement of segmental- and subsegmental bronchi, fixed hyperinflation ("mosaic pattern"), and deformed peripheral vessels [31, 67, 6, 80, 35, 58]. It is debatable, however, whether these signs are also typical for BO after hematopoietic stem cell transplantation. Some of these signs can only be interpreted correctly if sequential examinations have been performed. Furthermore, CT studies in children are rare. In BAL differential cytology the relative number of neutrophils is elevated [70]. The definite diagnosis of bronchiolitis obliterans can frequently only be achieved by open lung biopsy. The histopathological finding is bronchiolar inflammation with luminar scarring, fibrous tissue and obliteration of the small bronchioli without occluding the alveolar ducts. In lung function the small airways are affected first (hyperinflation) and there is exercise limitation without hypoxia. The involvement of vessels can vary. Therapeutically, systemic glucocorticosteroids, cyclophosphamide, azathioprine, chloroquine, glucocorticosteroid pulses, cyclosporine, anti-thymocyte globulin, tacrolimus, methotrexate, total lymphoid irradiation, thalidomide, clofazimine, extracorporal photopheresis, humanized monoclonal anti-IL-2 receptor antibodies are applied in BO without convincing success. Furthermore, there have been no controlled studies of any of the above-mentioned medications. As a number of interstitial diseases in childhood have shown a favourable response [22, 61, 59], our approach is to try to detect the disease at an incipient stage and use methylprednisolone pulse therapy as a first-line treatment (32). In about 30–50% of cases, at least a temporary response can be seen. Unfortunately, the time window for intervention is small in most cases and the speed of progression extremely variable, rendering evaluation of therapeutic success difficult. Complications of BO are pneumothorax, pneumomediastinum, bronchiectases, hypercapnia and pulmonary hypertension with cardiac failure.

Bronchiolitis Obliterans Organizing Pneumonia

The "bronchiolitis obliterans organizing peumonia" (BOOP), which occurs more rarely, was defined 1985 by Epler [24]. The etiology remains unclear. In the literature BOOP has been described in autoimmune diseases, after medication,as well as with viral and bacterial infection and as idiopathic BOOP [18]. Lately a number of cases have been published after HSCT with GVHD [44, 48, 74, 40]. There are also reports on early and fulminant courses [55, 16, 82]. The clinical picture is non-specific, with cough, dyspnea, and hypoxia. Lung function shows a restrictive pattern and impairied diffusion capacity. Histopathology demonstrates granulation – and fibrous tissue in terminal bronchioles reaching into alveoli – as well as interstitial lymphocytic inflammation. Cellular profiles of BAL show high lymphocyte counts, with low CD4/CD8-ratio (results from adults) [64]. Characteristic HR-CT-patterns in BOOP are ground-glass opacification and nodular shadows [29]. Typical bilateral, focal, predominantly peripheral infiltrates can be detected earlier using HR-CT rather than by X-ray of the thorax [51, 46]. In the literature (including patients after HSCT) the beneficial effect of treatment with glucocorticosteroids is emphasized beginning at an early stage and continuing for 6–12 months (18, 40, 44, 48, 50, 75).

Other Interstitial Lung Diseases

Bronchiolitis obliterans organizing pneumonia (BOOP) must be separated diagnostically from "lymphocytic interstitial pneumonia (LIP)", "diffuse alveolar damage" (DAD) and "lung fibrosis" as well as a NSID (nonspecific interstitial disease) and pulmonary veno-occlusive disease (42, 77, 3, 4). These diseases tend to occur after hematologic diseases, infections and therapeutical interventions (radiation, chemotherapy). Some of them are termed as late onset non specific interstitial lung disease (LONSILD). Prognosis varies greatly. Treatment modalities range from antioxidants to supportive care (oxygen) (72). With severe progression, the only chance for survival may be lung transplantation.

Post Transplant Lymphoproliferative Disease (PTLPD)

Post transplant lymphoproliferative disease (PTLPD) can manifest itself in the lung and can occur any time after transplantation. Frequency varies depending on the kind of transplantation, intensity and mode of immunosuppression, EBV-status of donor and recipient, and bone marrow reconstitution. Although rarely confined to the lung, the occurrence of this lesion together with other infections (like aspergillus) or GVHD makes diagnosis difficult, usually requiring an invasive approach. The WHO classification is not applied uniquely. Treatment modalities range from lowering immunosuppression to chemotherapy, using anti CD 20 antibodies to antiviral therapy, depending, among other factors, on histology, EBV-status, extent of the disease, and clinical course.

Lung Transplantation for Treatment of End-Stage Pulmonary Disease

Lung transplantation has been applied as ultima ratio in patients after an interval of up to 14 years after HSCT, mostly after pulmonary complications involving GVHD. The preferred surgical technique in most cases has been double lung transplant. Reported survival is similar to transplantation for other causes – with one patient surviving more than seven years [37]. Out of this series, one patient developed BOOP, a condition rarely seen after lung transplantation. A girl with a lobar transplant from the same living donor as her hematopoetic stem cells is the only known person without immunosuppression after lung transplantation [73]. Generally, prognosis after lung transplantation is a 45% survival rate after 5 years.

Consequences

Pulmonary complications after hematopoetic stem cell transplantation are poorly understood and treatment is unsatisfactory. There is no standardised pulmonary follow-up for children after hematopoetic stem cell transplantation with disappointing rates of pulmonary function measurements [23]. On the other hand, the spectrum of pulmonary complications is limited and the time sequence more or less known. Diagnostically it would seem essential to follow a scheduled plan of pulmonary surveillance measures including body plethysmography, assessment of gas exchange and exercise capacity as well as screening for infections. This should make it possible to gain insight into the pathogenesis of the diseases and examine whether bronchiolitis obliterans can be prevented by therapeutical measures at an early stage. As therapeutical options are limited in advanced BO, prophylaxis and preemptive therapy may be crucial. As a prerequisite, risk factors should be carefully studied and causal strategies developed in a multicenter approach.

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Allogeneic Hematopoietic Cell Transplantation for Inborn Metabolic Diseases

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Introduction

The treatment of inborn metabolic diseases such as lysosomal hydrolase deficiencies [21,32] and peroxisomal disorders such as adrenoleukodystrophy (ALD) [1,28] has been limited to symptomatic supportive care. Intravenous enzyme replacement has been largely ineffective, especially in storage diseases with central nervous system (CNS) manifestations. Allogeneic hematopoietic cell transplantation (HCT) with related or unrelated bone marrow cells, peripheral blood progenitor cells, or placental (umbilical cord) blood cells in these conditions repopulates recipient hematopoietic and lymphoid cells with metabolically normal donor-derived cells and thus provides a self-renewing source of hydrolase. In addition, HCT effectively repopulates mononuclear phagocytic cells, including macrophages, hepatic Kupffer cells, and pulmonary alveolar macrophages, in which substrate often accumulates in storage diseases. As discussed below, the repopulation of microglia with donor-derived cells after allogeneic HCT is a potentially important therapeutic mechanism of allogeneic HCT in patients with CNS manifestations of metabolic diseases.

Mechanisms of Metabolic Correction by HCT

Intercellular transport of lysosomal hydrolase from normal donor cells occurs by both receptor-mediated endocytosis and direct transfer of enzyme from adjacent cells [2]. The heterogeneity of receptor-mediated endocytosis systems limits the extent of hydrolase uptake among various cell types and tissues [38,40]. Direct intercellular transfer of hydrolase occurs independent of specific receptors but requires cell-to-cell contact and participation of adhesion molecules such as LFA-1 and -3, ICAM-1, -2, and –3, and CD2 (the sheep erythrocyte receptor on T lymphocytes) [2, 34]. Unlike lysosomal storage diseases, ALD is due to a defective protein component of the peroxisomal membrane that is neither secreted from normal cells nor transferred between cells, leading to defective oxidation and elevated plasma levels of very long chain fatty acids (VLCFAs) [30]. Co-culture with normal cells does not improve VLCFA oxidation by ALD fibroblasts, indicating that improvement of ALD after HCT is likely due to repopulation by metabolically normal cells instead of intracellular transfer of molecules from donor cells. Other beneficial effects of allogeneic HCT in ALD include normalization of plasma VLCFA levels and decreased perivascular inflammation.

Repopulation of Microglia after Allogeneic HCT

Microglia are the mononuclear phagocytic cells in the CNS [11, 24] and account for approximately 5% to 10% of non-neuronal cells in the brain. Activated microglia, also referred to as CNS macrophages, are involved in antigen presentation and responses to inflammation, infection, or CNS injury [11]. Microglia are derived from hematopoietic precursors that normally enter the brain from the peripheral circulation during embryonic and early postnatal life but not in adulthood [35]. In rodent HCT recipients, donor-derived cells can be identified throughout the CNS [12] and over time completely repopulate the microglial compartment [18, 22, 59]. In feline β-mannosidosis, these donor cells effectively transfer lysosomal hydrolase to recipient neurons in vivo [52]. After HCT, donor-derived cells also differentiate into other non-neuronal CNS cell populations such as astrocytes (also referred to as macroglia) [5, 31]. Postmortem studies confirm that donor mononuclear cells are also present throughout the brains of human allogeneic HCT recipients [51]. The kinetics of repopulation of microglia after HCT is slower than that observed with other mononuclear phagocytes like pulmonary alveolar macrophages and hepatic Kupffer cells [3, 25]. In humans, post-HCT repopulation with donor-derived microglia requires approximately 1 year, which may explain the ineffectiveness of allogeneic HCT in stabilizing or pre-

venting neurological deterioration in some rapidly progressive storage diseases [24, 25].

Animal Models in the Preclinical Evaluation of HCT for Inborn Metabolic Disorders

The availability of spontaneously occurring heritable animal models and the development of transgenic "knockout" lysosomal hydrolase deficient animals allows preclinical evaluation of the biochemical, physiological and clinical effects of allogeneic HCT in storage diseases. The most extensive studies of HCT in preclinical storage disease models have been in canine α-L-iduronidase deficiency (a model of mucopolysaccharidosis [MPS] IH, or Hurler syndrome) [3, 8, 45], murine β-galactosidase deficiency (a model of MPS VII, or Sly syndrome) [4, 42, 55], and murine galactosylceramidase deficiency (the "twitcher" mouse, a model of the sphingolipidosis globoid cell leukodystrophy [GCL]).

We have extensively studied HCT in the twitcher murine model [49], which most closely resembles Krabbe disease, the early infantile form of human GCL. HCT leads to prolonged survival, clinical improvement, attenuation of hindlimb paralysis [57, 58], remyelination in peripheral nerves and CNS [58], and stabilization of motor nerve conduction velocities [50] in presymptomatic twitcher mice but is of no benefit in symptomatic animals. After HCT, galactosylceramidase is present in the CNS and non-neural tissues [14, 60], and levels of the toxic metabolite psychosine (galactosylsphingosine) [15], are significantly decreased in the CNS [14]. Postnatal HCT is not curative in murine GCL, most likely because repopulation of the CNS and peripheral nervous system with donor cells does not occur rapidly enough to stabilize the progressive demyelination. Murine GCL may be an important model for critical evaluation of the effects of intrauterine cellular transplantation for infantile-onset sphingolipidosis.

Clinical Results

Several recent reports have summarized the results of allogeneic HCT for storage diseases and ALD [27, 44, 56]. This review will focus on current concepts of allogeneic HCT for MPS IH (Hurler syndrome), globoid cell leukodystrophy and ceramidase deficiency (Farber disease).

Mucopolysaccharidosis IH

The prognosis of untreated MPS IH (α-L-iduronidase deficiency) is poor, with a median survival of 4.5 years and with very few children surviving into the second decade of life [23]. In contrast, survival after HCT in children with MPS IH is 75% after bone marrow transplantation (BMT) from HLA-identical siblings, 53% after BMT from HLA-mismatched relatives, and 49% after BMT from unrelated donors [36, 37]. Hepatosplenomegaly, joint mobility, and upper airway obstruction in MPS IH resolve within months to a year after HCT. Corneal clouding stabilizes or slowly resolves [9], and visual acuity may improve even without regression of corneal clouding. Unfortunately HCT does not correct the skeletal manifestations (dysostosis multiplex) of MPS IH, which are due to metabolic dysfunction in chondrocytes and osteoblasts that arise from mesenchymal precursors. The orthopaedic complications of MPS IH require ongoing evaluation and surgical management even after HCT [7].

Mental retardation is a hallmark of untreated MPS IH [53], and both age and neurodevelopmental status are important determinants of outcome after HCT. When carried out in patients under age 2 years, HCT preserves neurocognitive function and prevents or reverses increased intracranial pressure. This favorable outcome is in part due to the fact that the developmental quotient (DQ) falls below 70 in most children with MPS IH after age 2 years [43]. In general, children with MPS IH with normal intelligence before HCT maintain that level of cognitive functioning after transplant [36, 43, 54], but those with significant neurocognitive impairment (e.g., DQ below 70) at HCT have progressive deterioration and do not benefit from the procedure.

Globoid cell leukodystrophy (GCL)

Globoid cell leukodystrophy (galactosylceramidase deficiency) is one of the sphingolipidoses, which are characterized by demyelination of the CNS and/or peripheral nervous system because of deficiencies in specific acid hydrolases involved in the metabolism of sphingomyelin, gangliosides and cerebrosides [48]. Characteristic globoid cells, derived from microglia or CNS macrophages and containing periodic acid-Schiff (PAS)-positive myelin breakdown material, are present in the brains, spinal cord and peripheral nerves. Interestingly, the widespread demyelination in GCL is due to accumulation of psychosine (galactosylsphingosine), which is derived from the substrate galactosylceramide and is toxic to both oligodendroglia and Schwann cells [15].

The four clinical phenotypes of human GCL vary in clinical manifestations and tempo of disease progression. Patients with early (age of onset, 3 to 6 months) or late (age of onset, 6 months to 3 years) infantile GCL have profound psychomotor retardation, failure to thrive, spasticity, seizures, optic atrophy and cortical blindness [10]. Juvenile GCL affects children from 3 to 10 years of age, with insidious onset and progression of visual loss, lower extremity spasticity, and in some patients dementia. Adult GCL occurs in patients over age 10 years and is characterized by slowly progressive difficulty in walking, long-tract signs, asymmetric weakness of the extremities, and difficulties with coordination and balance, but intellect is generally unaffected [20]. Allogeneic HCT is not curative in symptomatic early infantile GCL (Krabbe disease), in which neurodegeneration persists despite post-transplant biochemical improvement [23,26], analogous to observations in the preclinical studies of HCT in murine GCL. Although very limited experience suggests that presymptomatic infants with infantile GCL may benefit from HCT [26], early identification of the affected infant and of a suitable HCT donor are obvious practical challenges to this therapeutic strategy. The role for allogeneic HCT is more firmly established in patients with presymptomatic or minimally symptomatic juvenile or adult GCL, in whom HCT leads to stabilization and gradual improvement in clinical, neurological and neurocognitive status [13, 26, 43].

Ceramidase deficiency (Farber disease; lipogranulomatosis)

Of the six phenotypes of ceramidase deficiency [29], at least 50% of patients have the classic infantile form, or Farber disease phenotype. Affected infants have painful joint swelling, multiple painful subcutaneous nodules, hoarseness, swallowing difficulties, and failure to thrive [6]. Microscopic examination of the nodules shows granulomata containing ceramide-laden macrophages. Granulomata in the aerodigestive tract cause hoarseness and deglutition problems. Hepatomegaly, recurrent pulmonary infections and respiratory difficulties are common and due in large part to organ infiltration by ceramide-laden macrophages. Infants with Farber disease die with progressive and profound psychomotor retardation at a mean age of 18 to 20 months [29]. Two infants with Farber disease received allogeneic BMT at 18 months [47] and 9 months [61] of age, respectively. Subcutaneous nodules, joint pain and hoarseness regressed within 2 months after transplant in both patients. The older patient had progressive neurodegeneration and died 6 months after BMT. The younger patient, who had mild developmental delay and slight hypotonia at BMT, had progressive psychomotor retardation and graft failure, with a developmental age of 4 months at chronological age 32 months. Despite loss of donor cell engraftment, levels of ceramidase in the peripheral blood leukocytes remained in the donor heterozygous range, suggesting ongoing production of ceramidase by non-circulating donor cells and hydrolase uptake by recipient blood cells [61]. These limited observations indicate that HCT does not stabilize the rapid neurological deterioration in classic Farber disease.

New Therapeutic Approaches for Cellular Transplantation in Metabolic Diseases

Among new approaches for treatment of metabolic disorders by cellular transplantation, intrauterine HCT may be worthy of exploration, especially in the rapidly progressive infantile forms in which postnatal HCT is not effective. The major limitation to this approach is the low levels of donor cell engraftment, which may not provide sufficient hydrolase or metabolically active cells to correct the underlying biochemical defect [17]. Allogeneic HCT using reduced-intensity nonmyeloablative preparative regimens

may be considered in some indolent forms of storage diseases, providing gradual donor cell engraftment without the risk of aplasia and other short- and long-term toxicities associated with intensive marrow-lethal preparative regimens [19, 46]. The use of these regimens is not feasible in more aggressive forms of storage diseases. Insertion of genes for specific lysosomal hydrolases or for the ALD protein into autologous hematopoietic stem cells (HSCs) and transplantation of these cells is theoretically very attractive but remains at the level of preclinical investigation at this time because of ongoing challenges such as efficient introduction and integration of the exogenous gene in truly primitive HSCs and sustained, consistent high-level expression of the hydrolase in these cells and their progeny [41]. A potentially exciting approach for storage diseases with skeletal manifestations (dysostosis multiplex) is the co-transplantation of mesenchymal stem cells (MSCs), which may differentiate into chondrocytes and osteoblasts [33, 39]. Although clearly not a clinical therapeutic option at this time, intracerebral injection of MSCs may favorably affect the neuropathological and biochemical abnormalities in a murine model of acid sphingomyelinase deficiency (Niemann-Pick disease types A and B) [16].

Summary

Clinical experience for more than two decades has shown that allogeneic HCT may benefit some but not all patients with inherited metabolic diseases. The HCT procedure is most effective in presymptomatic patients and those with indolent forms of storage diseases but is ineffective in those with overt neurological symptoms or aggressive neonatal or infantile forms. HCT alone does not correct skeletal dysplasia in MPSs and may not prevent development or progression of the peripheral neuropathy in sphingolipidoses and ALD. Decisions regarding HCT in patients with storage diseases should be made by investigators knowledgeable about these diseases, with judicious use of laboratory and clinical resources necessary to reach the best therapeutic decision for the individual patient.

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