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Last Marrow Standing: Bone Marrow Transplantation for Acquired Bone Marrow Failure Conditions

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Abstract

Paroxysmal nocturnal hemoglobinuria, aplastic anemia, and myelodysplastic syndrome are a spectrum of acquired marrow failure, having a common pathologic thread of both immune dysregulation and the development of abnormal hematopoiesis. Allogeneic hematopoietic cell transplantation plays a critical role in the treatment of these disorders and, for many patients is the only treatment modality with demonstrated curative potential. In recent years, there have been many breakthroughs in the understanding of the pathogenesis of these uncommon disorders. The subsequent advances in nontransplant therapies, along with concurrent improvement in outcomes after hematopoietic cell transplantation, necessitate continual appraisal of the indications, timing, and approaches to transplantation for acquired marrow failure syndromes. We review here contemporary and critical new findings driving current treatment decisions.

Keywords

Bone marrow transplant; Myelodysplastic syndrome; Aplastic anemia; Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria

Introduction

Complement-mediated hemolysis is the central clinical feature of Paroxysmal nocturnal hemoglobinuria (PNH) and, in fact, led to discovery of the alternative pathway and characterization of complement regulatory proteins. Although recent years have seen the development of targeted anti-hemolytic therapy, PNH is a clonal hematopoietic disorder, and HCT remains the only curative therapy. With several overlapping features between PNH and myelodysplastic syndrome (MDS), the diagnosis must be confirmed, particularly when considering transplantation. On a bone marrow aspirate, PNH can often have dysplastic-appearing morphologic changes [1]. Conversely, small PNH clones are often present in patients with MDS. Clinical features and advanced diagnostics (cytogenetic, molecular, and flow cytometric studies) are relied upon to discriminate between the two diagnoses [2]. Unlike MDS, it has been well documented that PNH clones lack intrinsic growth advantages over those with normal phenotype; rather, they are postulated to have an immunologic advantage leading to their dominance in the marrow [3–5]. Successful transplantation may be less of a matter of elimination or reduction of the PNH clone, but more a process of

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supplying normal hematopoietic cells and replacing or resetting the immune system, effectively tipping the balance between the PNH clone and normal hematopoietic stem cell. With less emphasis on clone reduction, reduced-intensity conditioning (RIC) has been pursued with the aim of reducing transplant-related toxicity seen with intensive conditioning regimens.

The Current Transplant Experience

The Gruppo Italiano Trapianto Midollo Osseo (GITMO) reported the outcomes of 26 patients who underwent transplantation between 1998 and 2006 for PNH [6]. At 1 year, the transplant-related mortality was 26% in the 15 patients conditioned with a myeloablative (MA) regimen as opposed to 63% in the 11 patients conditioned with RIC regimens. The authors attributed a proportion of the increased mortality with RIC to the fact that all three patients in the study without an HLA-matched donor were in the RIC group. In a univariate analysis of the 23 patients who had an HLA-matched donor, there was no difference in 5-year disease-free survival when comparing MA to RIC regimens (73% and 47% respectively, $p = 0.31$). Elimination of the clone appeared to be durable as the 15 patients with hematologic recovery after HCT had no evidence of PNH at a median follow-up of 131 (range 30–240) months. The Seattle group updated the results of 19 patients conditioned with 90 mg/m² fludarabine and 200 cGy total body irradiation, 4 of which had HLA-mismatched unrelated donors [7]. All but two patients (89.5%) had a sustained engraftment. At the time of last follow-up, 15 (78.9%) were alive without any evidence of the presence of a PNH clone.

Transplant versus No Transplant

Since PNH is not perceived to be as imminently life threatening, the timing of HCT in the course of care for patients with PNH contrasts with that of aplastic anemia or acute myeloid leukemia. Transplant too early and a patient will be exposed to undue toxicity and early mortality as a result of the procedure. Wait too long and the patient may develop complications from PNH rendering HCT unfeasible. Currently, there is an absence of a validated risk stratification system to identify those at high risk of developing complications and guiding the optimal timing of HCT for patients with PNH. The European Group for Blood and Marrow Transplantation (EBMT) Group and the French Society of Hematology (SFH) recently reported the results of a transplant versus no transplant matched comparison study [8]. Outcomes were measured from the appearance of a PNH-related life-threatening complication (development of severe aplastic anemia [sAA] or thromboembolism). Patients were matched on type, severity, and year of the complication, as well as age, and the time from diagnosis to the complication. Ultimately, 24 pairs of patients with thromboembolism and 30 pairs with sAA were available for matched analysis. For patients with thromboembolism, it was found that those who underwent HCT had a worse overall survival (hazard ratio = 10.0 [95% CI, 1.3–78.1]) as compared to those who did not undergo HCT. In a subsequent global matching analysis, two prognostic strata were derived based on age and time from diagnosis to thromboembolism. When adjusting for the strata, HCT was associated with a similar overall survival for patients in the higher-risk stratum, and with a lower overall survival in the lower-risk stratum (Table 1). In the matched pairs who underwent HCT for sAA, there was a non-significant trend towards worse overall survival with transplantation (HR = 4.0 [95% CI 0.9–18.9]). The global matching analysis was not completed with these pairs as the procedure led to too many strata.

The development of eculizumab, an inhibitor of complement protein 5 (C5), has had a dramatic impact on the indications for HCT. At a median follow up of 39 months, the overall survival was not different in a study of 79 consecutive patients treated with eculizumab as compared to age- and sex-matched normal controls ($p = 0.46$) [9]. However,

when compared to 30 similar patients managed before the approval of eculizumab, there was a significant survival advantage seen in those treated with eculizumab (estimated 5-year overall survival 66.8% versus 95.5%, $p = 0.03$). Three patients on eculizumab, all over 50 years old, died of causes unrelated to PNH.

Transplant in the Eculizumab Era

Revised indications for HCT in the eculizumab era would include repeated breakthrough hemolysis or thrombosis while on eculizumab. Furthermore, patients who present with or develop another marrow failure syndrome (sAA or MDS) would be considered candidates for HCT based on the severity of marrow failure. Despite inhibition of C5, some patients treated with eculizumab continue to experience severe extravascular hemolysis as a result of increased clearance of C3 fragment coated PNH red cells by complement receptors within the reticuloendothelial system. These patients could be considered for HCT, although inhibition of C3 fragment accumulation in the near future may render this indication obsolete [10]. Nonetheless, there is a remaining proportion of patients with PNH who will derive benefit from HCT. Therefore, continued efforts are needed to identify conditioning regimens with the lowest toxicity that will durably extinguish the PNH clone.

Aplastic Anemia

Introduction

Aplastic anemia (AA), a life-threatening disorder of marrow hypoplasia and peripheral blood cytopenias, is considered severe (sAA) if marrow production is inadequate in two cell lines, and very severe (vsAA) if the neutrophil count is $< 0.2 \times 10^9/L$. Although the pathophysiology of AA is not completely understood, the response to immunosuppressive therapy (IST) supports the putative autoimmune injury of bloodforming elements. Historically, there has been a steady increase in the success of IST in patients with sAA, with a response rate and 5-year overall survival both now approaching 80% [11]. However, this improvement has plateaued in the past 20 years, and a significant proportion of patients will fail to respond or will relapse shortly after an initial response. It is unclear if immune suppression is inadequate in these patients or if there is a different pathologic process leading to marrow failure such as hypoplastic MDS or an occult hereditary defect.

Although the complication rates of transplantation in AA have also improved over time, graft rejection (5%–10%) and GVHD (acute 12%–30%, chronic 30%–40%) remain a problem. Since the presumed pathologic mechanism in AA is immune injury to the marrow, a graft-versus-leukemia (GVL) effect is not needed, and transplant parameters including conditioning, graft source, and donor type should be optimized to reduce HCT-related toxicity, graft vs. host disease (GVHD), and graft rejection. Still, failure in the form of graft rejection is not always a poor outcome in AA. Although uncommon, some patients undergo autologous reconstitution after allogeneic HCT and experience better outcomes than their cohorts with allogeneic reconstitution [12]. This phenomenon further underscores the underlying autoimmune etiology of AA and the lack of need for a GVL effect.

Unfortunately, most patients have acquired a critical degree of stem cell damage over the course of their disease, requiring an infusion of allogeneic stem cells. Choosing IST versus HCT as primary therapy for sAA or vsAA is largely based on the availability of a matched sibling donor and patient age. Similar to IST, younger patients who undergo matched-sibling HCT have good outcomes with long-term survival rates of 70–80%, as both age and non-related donors are associated with a worse outcome [13]. Therefore, the current recommendation is for HCT upfront in patients under the age of 40 with a matched sibling donor, and IST is the preferred first-line treatment for those over the age of 40 or without a matched sibling donor [14].

New Approaches in Conditioning

Cyclophosphamide with or without ATG followed by post-HCT methotrexate and cyclosporine has long been used for conditioning in patients with sAA [15]. Novel conditioning regimens aimed at to reducing rates of HCT-related complications have shown promise. March and colleagues reported the results of 50 patients who underwent HCT after conditioning with fludarabine (30 mg/m² for 4 days), cyclophosphamide (300 mg/m² for 4 days), and dose-escalated alemtuzumab (median 60, range 40–100 mg) [16]. One in four patients was over the age of 50, 58% received their graft from an unrelated donor, and 66% had previously received ATG. The cumulative incidence of graft failure was 9.5% for matched related and 14.5% for unrelated donor HCT. Severe (grade III/IV) acute GVHD was not observed, and only two patients developed chronic GVHD. The cumulative incidence of acute and chronic GVHD at 1 year was 16.5% and 7%, respectively. A concern with incorporating alemtuzumab into conditioning is an increase in viral infections; however, this was not observed. With a median follow up of 18.2 months, the actuarial overall survival at 2 years for all patients was 88%. Survival was strongly associated with comorbidities. For patients with a comorbidity score of 0-1, the 2-year OS was 95% compared with only 42% with a score of ≥ 2 ($p < 0.001$). Although graft rejection rates were similar to what is observed with other commonly used conditioning regimens, in this study there was an excellent overall survival and a significantly lower incidence of GVHD despite a large number of patients being over the age of 50 or undergoing unrelated donor HCT.

Bone Marrow versus Peripheral Blood

Prior to the development of cellular apheresis techniques, HCT was carried out with harvested bone marrow as the graft source. Although growth factor mobilized peripheral blood grafts are now commonly used in HCT, not all grafts are created equal. Peripheral blood grafts tend to contain more committed progenitors as well as a higher ratio of T-cells to CD34+ cells as compared to marrow grafts, leading to potential differences in reconstitution and rates of GVHD. A series of studies have established marrow stem cells as the preferred graft source over peripheral stem cells in both matched sibling and unrelated transplantation for patients with AA [17]. A significant survival advantage was seen in all four studies with a long-term survival ranging from 72–80% for marrow versus 61–76% for peripheral stem cells (Table 2). Peripheral blood stem cells (PBSC) were associated with a higher risk of acute GVHD across studies, and higher rates of chronic GVHD were seen with PBSC in matched sibling transplants. Although these studies establish bone marrow as the preferred graft, PBSC could be considered in patients that experience graft rejection with their first HCT and in those with donors who are at high-risk for complications from the anesthesia required for bone marrow harvest.

Expanding the Donor Pool

In published guidelines [14], a main consideration for HCT is the availability of a matched related donor. Previously, transplantation with donors other than matched siblings (alternative donors) had significantly worse outcomes largely due to increased rates of graft rejection and GVHD [18]. More recently, improvements in conditioning regimens, post-transplant immunosuppression, and supportive care have resulted in improved outcomes after alternative donor HCT. Bacigalupo and colleagues analyzed the results of 100 patients who underwent alternative donor HCT after failed IST [19]. Patients were conditioned with fludarabine, cyclophosphamide and ATG with or without 2 Gy total body irradiation. The estimated 5-year overall survival for all patients was 75%, and 83% among those who were transplanted after 2004.

Kim and colleagues reported a registry study of 225 patients who underwent HCT for aplastic anemia (92.5% with sAA or vsAA) between 1995 and 2008 [20]. Patients with

matched related donors demonstrated lower rates of treatment-related mortality (19.1% versus 39.7%, $p = 0.001$) and graft failure, as well as a better 5-year survival (76.6 versus 56.8%, $p < 0.001$) when compared to alternative donors. Although the overall incidence of acute GVHD was higher in the matched related donor group (7.8% versus 32.9%, $p = 0.01$), there was no difference in the incidence of severe (grades III/IV) acute or chronic GVHD. Patients who underwent matched related donor HCT were more likely to be under the age of 31, have a time from diagnosis to HCT of less than 6 months, and to have received prior IST. The investigators then conducted a case-control analysis to compare donor source using propensity score matching based on patient and transplant characteristics. They identified 25 matched pairs who underwent either matched related or alternative donor HCT. There was no significant difference in overall survival, treatment related mortality, and the incidences of GVHD and graft failure between the two groups. The finding of similar outcomes in matched related and alternative donor transplantation adds to the mounting evidence that patients who have an available donor, regardless of relatedness, should be considered earlier for HCT.

Despite the more than 14 million adults registered with donor registries worldwide, only 60% of patients of Caucasian descent, and considerably less for non-Caucasians, will have an available and fully matched unrelated adult donor. Therefore, other donor sources such as umbilical cord blood have been explored in an attempt to extend HCT to candidate patients without a matched donor. While umbilical cord blood allows transplantation with greater donor-recipient HLA disparity without excessive risk of GVHD, it does so at the cost of delayed engraftment and an increased risk of graft failure when compared to adult donor grafts. An analysis by Eurocord and the EBMT reported engraftment and 3-year survival rates of only 51% and 38%, respectively [21]. Results were heavily influenced by cell dose where a total nucleated cell dose of $> 3.9 \times 10^7/\text{kg}$ was associated with better engraftment (HR for engraftment = 1.5, 95% CI 1–2.2) and survival (HR for death = 0.39, 95% CI 0.2–0.78). Gormley et al. recently reported an intriguing study of 8 patients that underwent co-infusion of a single umbilical cord blood unit with CD34+ selected cells from a haploidentical relative [22]. All of the patients engrafted neutrophils by day 42, and at a median follow up of 9 months, 7 patients were alive (one death as a result of CMV pneumonitis). Only one patient failed to achieve sustained engraftment from the umbilical cord unit and recovered from the haploidentical donor.

Myelodysplastic Syndrome

Introduction

At the time of their diagnosis, a majority of patients with MDS are over the age of 65 years. As a result, the care of these patients is often complicated by medical comorbidities, and treatment considerations revolve around a balance of the benefit and tolerability of a given modality. Further complicating therapeutic decisions is considerable disease heterogeneity with a spectrum of presentation ranging from an indolent course over several years to rapid progression to acute myeloid leukemia (AML). Although advances have been made in recent years in the treatment of MDS, allogeneic HCT remains the only known cure. Consequently critical questions center on who should be considered for HCT, and when in their disease course. Since its original publication in 1997, the International Prognostic Scoring System (IPSS) has become the most widely used prognostic classification system for MDS segregating patients into four risk strata (low, intermediate-1, intermediate-2, high) based on the number of peripheral cytopenias, cytogenetics, and percentage of bone marrow blasts [23]. Cutler and colleagues conducted a Markov analysis concluding that patients with MDS categorized as intermediate-2 or high risk had the best life expectancy if transplanted early after diagnosis, whereas more conservative management appeared appropriate in patients with low and intermediate-1 risk disease [24]. Since that time, there has been

continued refinement in our understanding of the genetic heterogeneity of MDS and the application of this understanding to disease risk profiling.

Refining Disease Risk

Within the scoring system, the IPSS places a higher weight on blast percentage as compared to cytogenetics. Accumulating data on the prognostic power of different cytogenetic abnormalities suggests that the IPSS significantly underweights their impact [25,26]. A refined comprehensive cytogenetic classification system has been proposed based on an international data collection of 2,902 patients across 4 databases, 45% of which had cytogenetic abnormalities [27]. Although patients with chronic myelomonocytic leukemia were included, those with secondary MDS were not. On the basis of their mean coefficients, the cytogenetic findings were divided into five separable risk groups, and the limits for the risk groups were equally spaced. The score was validated by both an internal bootstrapping analysis and on an external cohort. Major changes from the IPSS include separating the very good (–Y, del(11q)) from the good and the segregation of those with and a dismal prognosis (≥ 3 abnormalities) within the very poor group. Although this schema demonstrates better discrimination between risk groups, it does not incorporate the ever-growing library of mutations identified by molecular diagnostics. Additionally, it is more cumbersome to use than the original IPSS. Nonetheless this cytogenetic classification schema is a sizeable step forward and it will be included in the highly anticipated revision of the IPSS (IPSS-R).

The optimal timing and section for HCT is a moving target. Since the Markov analysis by Cutler and colleagues, we have not only gained a better understanding of disease risk, but outcomes after HCT have improved over time [28]. What remains clear is that the GVL effect is capable of maintaining long-term remissions in patients with myeloid disorders [29]. However relapse, being the most common cause for failure after HCT, continues to be a problem [30]. Relapse rates after HCT were 41% after RIC, and 33% after myeloablative conditioning in 1,333 patients over the age of 50 reported to the EBMT [31]. Given their advanced age and medical comorbidities, patients with MDS are often relegated to conditioning with RIC that has minimal anti-MDS activity. Therefore, two strategies have been used to reduce post-HCT relapse: pre-HCT cyto-reduction, and post-HCT maintenance.

Pre-transplant Cyto-reduction

Despite a lack of evidence confirming efficacy, the use of pre-HCT cyto-reductive therapy has become common practice. Over the past three years, 130 of 141 patients (92%) transplanted for MDS at our institution received prior chemotherapy (unpublished data courtesy of H. Joachim Deeg). Prior to 2004, the mainstay of cyto-reduction was intensive chemotherapy regimens developed as induction therapy for AML; though retrospective studies of these regimens before HCT have not pointed to a clear benefit [32–34]. Furthermore, intensive pre-HCT therapy may lead to a worsening in performance status impacting patients' candidacy for and capacity to tolerate the subsequent HCT [35]. More recently, hypomethylating agents (azacitidine and decitabine) have increasingly been used for pre-HCT cyto-reduction, rendered attractive by their ease of administration and a low toxicity profile, in an attempt to better balance cyto-reduction and treatment-related toxicity. In the absence of prospective data, several groups have published the results of retrospective analyses, noting the feasibility of this approach [36]. We reported our experience in 68 patients who underwent HCT for MDS who received either induction chemotherapy or azacitidine prior to HCT [37]. The 1-year overall survival was 57% in the azacitidine group and 36% in the group given induction chemotherapy. Although the risk of post-HCT relapse and non-relapse mortality was lower in the azacitidine group, none of the differences were statistically significant, suggesting that at a minimum azacitidine did not confer worse outcomes when compared to induction chemotherapy.

Post-transplant Maintenance

An alternative strategy to reduce post-HCT relapse is the initiation of maintenance therapy after engraftment. In the race for dominance between the recipient's MDS clone and donor graft's GVL effect, maintenance therapy could slow the MDS clone allowing more time for the GVL's eradication efforts. Similar to pre-HCT therapy, azacitidine has been explored given its favorable toxicity profile and rapid marrow recovery after treatment. In a phase I dose-finding study, de Lima and colleagues evaluated low-dose azacitidine as post-HCT maintenance in 45 patients with high-risk AML and MDS [38]. At a median follow-up of 20.5 months, 24 (53%) patients had developed disease recurrence. The 1-year event-free and overall survival was 58% and 77%, respectively. The RELapse prevention with AZAcitidine (RELAZA) trial prospectively treated 20 patients with full-dose azacitidine (75 mg/m²/day for 7 days), after screening identified imminent relapse (donor CD34+ chimerism <80% in the absence of morphologic relapse) at a median of 169 days after HCT [39]. Sixteen patients responded with an increase in CD34+ donor chimerism or stabilization at 80% after a single cycle of azacitidine. Eleven patients went on to receive additional cycles (median 4, range 1–11). Morphologic relapse eventually occurred in 13 patients, but was delayed by a median of 7.6 months after the initial documentation of imminent relapse. These studies demonstrate that the strategy of post-HCT maintenance or pre-emptive azacitidine treatment is associated with an acceptable safety profile and may be effective in delaying or even preventing morphologic relapse. Azacitidine may also manipulate the delicate balance between GVHD and GVL by expanding immunomodulatory T regulatory cells mitigating GVHD, and up-regulate the expression of tumor antigens bolstering the GVL effect [40]. In the study by de Lima et al., it was noted that the probability of developing chronic GVHD decreased significantly with the number of azacitidine cycles [38]. Dennis et al. recently reported the expansion of T-regulatory cells in 27 patients treated with azacitidine post-HCT as compared to a time-matched control population [41]. Although a cytotoxic T-cell response to candidate cancer antigens was present in 1 of 22 patients pre-HCT, circulating antigen-specific cytotoxic T cells were detected in 14 of 16 patients who had received a minimum of 6 cycles of azacitidine.

The MDS Treatment Package

The treatment landscape for MDS is ever-changing as prognostic scores, supportive care, therapies improve over time. Treatment decisions for patients with MDS, who are HCT candidates, should be made while considering the entire treatment package including pre-HCT therapy, conditioning regimen, and potential post-HCT treatment, be it anticipatory or therapeutic (Figure 1). However, much work remains on identifying the appropriate intervention for each phase of the treatment arc and interactions between each treatment decision made along the way.

Conclusion

Study of the acquired marrow syndromes PNH, aplastic anemia, and MDS presents a set of distinct challenges, which only compound when considering transplantation. The first is the rarity of these disorders. The annual incidence of PNH, aplastic anemia, and MDS is estimated to be 0.13, 0.2, and 7 per 100,000 per year respectively. The advanced age of most patients with acquired aplastic anemia and MDS may lead to ineligibility for studies as a result of comorbidities. Past successes (such as 70–80% long-term survival after IST for sAA) can be difficult to improve upon, as the probability of proving superiority of any new treatment is inversely proportional to the success of the old standard. Nonetheless, over the course of the past decade there have been significant advances in both the transplant and non-transplant treatment of these disorders. Allogeneic HCT remains the only approach with curative potential for many patients. With the success of new agents, such as eculizumab in

PNH, and better understanding of disease-risk factors, such as cytogenetics in MDS, the indications for and optimal timing of HCT are changing. For patients with PNH in the eculizumab era, HCT is reserved for those that are intolerant, develop concurrent marrow failure (MDS or aplasia), or have continued complications despite eculizumab administration. Continued reduction transplant-related toxicity and improved outcomes with unrelated donors are beginning to expand the front-line role of HCT in aplastic anemia. Better prognostic tools in MDS are being used to determine who and when patients should be considered for HCT, while efforts to reduce post-HCT relapse include pre-HCT cyto-reduction and post-HCT anticipatory therapy.

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Figure 1.
The management of myelodysplastic syndrome as a treatment package

Table 1

Overall survival in patients in transplanted versus non-transplanted patients after thromboembolism [8]

Prognostic strata	Number of patients	Hazard ratio	95% Confidence interval
<i>No-HCT</i>			
Stratum A	33	1	
Stratum B	6	5.8	1.2 – 28.9
<i>HCT</i>			
Strata A+B	41	4.1	1.2 – 13.8

Stratum A: age < 30 and time from diagnosis of PNH to thromboembolism > 3 months, or time from diagnosis to thromboembolism < 3 months

Stratum B: age ≥ 30 and time from diagnosis of PNH to thromboembolism > 3 months

Table 2

Peripheral blood versus bone marrow grafts in matched sibling transplantation for aplastic anemia

Parameter	OS (p value)	aGVHD	cGVHD
<i>Schrezenmeier et al. 2007</i> [42]			
BM	64% (0.119) ^{*†}	20%	31%
PBSC	52%	19%	30%
<i>Chu et al. 2011</i> [43]			
BM	80% (0.212) [†]	13%	16%
PBSC	76%	28%	43%
<i>Eapen et al. 2011</i> [44]			
BM	76% (0.02) [†]	31%	40%
PBSC	61%	48%	58%
<i>Bacigalupo et al. 2012</i> [17]			
BM	74% (0.001) ^{*#}	11%	11%
PBSC	64%	17%	22%

* Patients over the age of 20 only

[†] 3-year estimate

[†] 5-year estimate

[#] 10-year estimate

BM = Bone marrow, PBSC = Peripherally collected stem cells, OS = Overall survival, aGVHD = Cumulative incidence of grade 2/4 acute graft-versus-host-disease, cGVHD = Cumulative incidence of chronic graft-versus-host-disease