Best Practice & Research Clinical Haematology 32 (2019) 101108

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/issn/15216926

Transplantation without pretransplant therapy: Is this a possibility? Insights into providing transplantation at diagnosis for patients with acute leukemia

Nelson J. Chao

Division of Cell Therapy in the Department of Medicine, Duke University School of Medicine, 200 Pratt Street, Durham, NC, 27705, USA

ARTICLE INFO

Keywords:
Acute myeloid leukemia
AML
Hematopoietic stem cell transplantation
HSCT
Minimal residual disease
MRD
Myelodysplastic syndromes
MDS

ABSTRACT

Allogeneic hematopoietic stem cell transplantation (HSCT) has the potential for providing a cure for several hematologic malignancies. Although in most circumstances, allogeneic HSCT is preceded by disease-directed or cytoreductive therapy, it is unclear if these toxic conditioning regimens can be circumvented. This review summarizes evidence that will provide insights into factors that influence outcomes in allogeneic HSCT and whether this curative therapy could be used right at diagnosis.

Introduction

Hematopoietic stem cell transplantation (HSCT) is widely performed for the treatment of lymphoma, leukemia, and myelodysplastic and myeloproliferative syndromes. Most patients generally receive intensive myeloablative therapy before HSCT, which is followed by a stem cell "rescue." In allogeneic HSCT, human leukocyte antigen (HLA)-matched stem cells derived from a donor are transplanted into myeloablated patients or recipients which have the ability to self-renew and differentiate into functional progeny of various specialized cells. For the HSCT to be successful, the transplanted stem cells need to engraft in the appropriate microenvironment and bone marrow niches of the recipient. In addition, an optimal amount of stem cells, facilitator cells, adequate homing, ABO compatibility, low immune suppression in the donor, certain genetic factors, and proper storage, are necessary to achieve desired outcomes for allogeneic HSCT. Similarly, recipients of allogeneic HSCT need to be adequately prepared and factors such as adequate immune suppression, HLA matching, disease status, microbiome and optimal stromal support, can influence outcomes [1]. Indeed, for most hematologic malignancies, allogeneic HSCT is only considered based on a risk–benefit ratio, beyond first remission, and after failure of initial therapy. For instance, among patients with favorable-risk acute myeloid leukemia (AML), pediatric acute lymphoproliferative leukemia (ALL), standard-risk adult ALL, and other lymphoproliferative diseases (Hodgkin lymphoma, non-Hodgkin lymphoma), allogeneic HSCT is provided after disease-directed therapy. On the other hand, in certain situations or conditions, patients sometimes directly undergo HSCT without any disease-directed therapy. These situations are usually where transplantation is serving primarily as a means to correct normal hematopoiesis or immune function, conditions or diseases that have no effective therapies, and malignancies whose cure with transplantation is primarily dependent on graft-versus-leukemia effects. The examples of diseases/conditions sometimes transplanted without any disease-directed therapy are hemoglobinopathies, immune deficiencies, metabolic disorders, aplastic anemia, low-grade lymphomas, myelodysplasia, and certain myeloproliferative

E-mail address: nelson.chao@duke.edu.

https://doi.org/10.1016/j.beha.2019.101108

Table 1
Impact of conditioning intensity on transplant outcome for AML/MDS [4].

Conditioning regimen	Overall Survival	Relapse	Relapse-free survival	TRM
Myeloablative	77.5%	13.5%	67.8%	15.8%
Reduced intensity	67.7%	48.3%	47.3%	4.4%
P value				.002

Survival, relapse, relapse-free survival (probability), and transplant-related mortality at 18 months. There was more graft-versus-host disease with myeloablative conditioning.

neoplasms. This paper examines evidence to determine whether allogeneic HSCT can be performed successfully among patients with leukemia at diagnosis or before pretransplant disease-directed therapy.

Factors influencing HSCT outcomes in leukemia

It is well-known that low disease burden during allogeneic HSCT correlates with better outcomes. Notably, patients in complete remission are more likely to have favorable outcomes as compared with those in partial remission or progressive disease [2]. A retrospective study that examined patients with AML who underwent allogeneic HSCT showed that the absence of minimal residual disease (MRD) during transplantation was associated with improved survival and lower incidence of relapse. Importantly, lower survival and higher relapse rates were reported among patients who were MRD-positive and among those who had active disease during allogeneic HSCT [3]. Since high intensity myeloablative conditioning regimens before allogeneic HSCT in AML are known to cause considerable toxicity and increased treatment-related mortality, reduced intensity conditioning regimens have been developed and studied among patients with AML. The BMT CTN 0901 study compared outcomes among patients with AML or myelodysplastic syndromes (MDS) who received either myeloablative conditioning or reduced intensity conditioning regimens before allogeneic HSCT. As shown in Table 1, while overall survival was higher among patients receiving myeloablative conditioning, significantly high relapse rates were reported for patients who received reduced intensity conditioning. In addition, although reduced intensity conditioning was associated with lower treatment-related mortality, myeloablative conditioning provided a statistically significant advantage for relapse-free survival [4]. Given these two studies, Walter et al. determined the impact of a preparative regimen in influencing outcomes among patients based on MRD status. In this study, MRD positivity, irrespective of the intensity of the conditioning regimen correlated with an increased incidence of relapse, thereby confirming the negative impact of MRD on relapse risk in allogeneic HSCT (Fig. 1) [5]. However, only mutations in the RAS pathway have been shown to correlate with an increased probability of relapse among patients who received reduced intensity conditioning as compared to those who received myeloablative conditioning regimens [6]. Taken together, these studies indicate that MRD status remains the single-most predictive criterion for influencing outcomes in allogeneic HSCT in leukemia.

Factors influencing HSCT outcomes in MDS and myelofibrosis

As is the case among patients with leukemia, transplantation outcomes in MDS are better among patients who have a lower

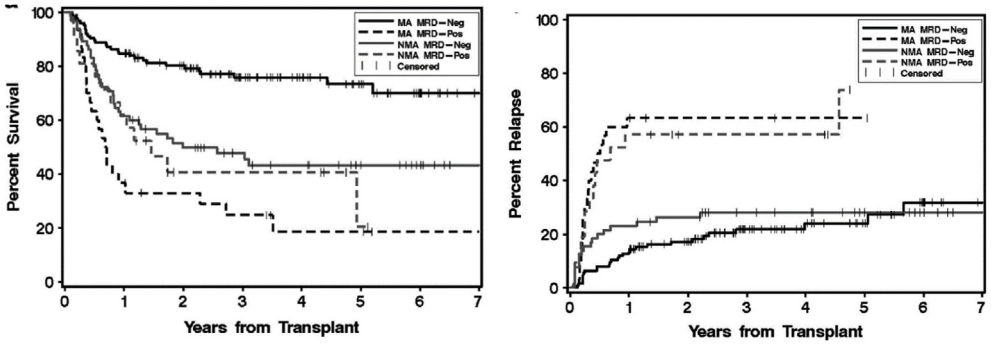

Fig. 1. Impact of preparative regimen on outcome of MRD- and MRD + patients [5].
Panel on the right (relapse) suggests dose intensity does not compensate for MRD.
Dark black solid line = myeloablative conditioning MRD-negative.
Medium black solid line = non-myeloablative condition MRD-negative.
Dark black dashed line = myeloablative conditioning MRD-positive.
Medium black dashed line – nonmyeloablative condition MRD-positive.
Reprinted by permission from SpringerNature: *Leukemia*, Comparison of minimal residual disease as outcome predictor for AML patients in first complete remission undergoing myeloablative or nonmyeloablative allogeneic hematopoietic cell transplantation. Walter RB, Gyurkocza B, Storer BE, Godwin CD, Pagel JM, Buckley SA, et al. © 2015.

Table 2
Microtransplantation-associated outcomes among elderly patients with AML [14].

	Low-risk group	Intermediate-risk group	*P* value
Leukemia-free survival	84.4%	59.2%	.272
Overall survival	89.5%	65.2%	.308
	High T-cell dose	Low T-cell dose	
Leukemia-free survival	76.4%	49.5%	.091
Overall survival	82.1%	55.3%	.041

Six-year survival rates were not significantly different between the risk groups. Survival rates in patients with a high dose of donor T cells ($> 1.1 \times 108$/kg) for each course were significantly higher than for patients who received a lower dose.

pretransplant disease burden. Similarly, improved relapse-free survival and lower relapse rates have been reported for patients with either a complete remission or < 5% blasts compared to those with 5%–20% blasts [7]. On the other hand, high-risk category, as defined by the revised International Prognostic Scoring System, has been associated with a lower overall survival rate and a key factor in predicting transplantation failure in MDS [8]. A previous Japanese study reported that complete remission with induction chemotherapy and no chemotherapy led to similar outcomes, but a lack of response to chemotherapy was associated with poorer survival among patients with advanced MDS after allogeneic HSCT [9]. Notably, in MDS, no significant differences have been observed in allogeneic HSCT outcomes with or without hypomethylating therapy before transplantation and between induction chemotherapy versus hypomethylating therapy before allogeneic HSCT [10,11]. Among patients with myelofibrosis, those who responded to JAK1/2 inhibitors were associated with improved overall survival as compared to those who were nonresponders to JAK1/2 inhibitor therapy before allogeneic HSCT; however, the evidence is not statistically significant [12]. Based on these studies, the appropriate pretransplantation disease-directed therapy or regimen remains uncertain for MDS and myelofibrosis. An important consideration for allogeneic HSCT in MDS is the availability of a donor and risks versus benefits of hypomethylating therapy pretransplantation.

Is HSCT doable without conditioning?

To determine whether allogeneic HSCT can be performed at diagnosis, clinical trials that compare upfront HSCT versus pretransplant therapy followed by HSCT need to be carried out. Such studies, however, can never be executed and hence the answer may not be clearly determined. Recent studies using microtransplantation suggest that transplantation could be successful without conditioning or preparative regimens [13]. Microtransplantation involves no conditioning other than using granulocyte colony-stimulating factor–mobilized haploidentical peripheral blood progenitor cells which are infused after three consecutive cycles of high-dose cytarabine consolidation therapy for patients with AML in first complete remission. This novel transplantation technique was also associated with improved leukemia-free and overall survival (Table 2) [14]. Additional trials to further investigate this approach are ongoing and eagerly anticipated [15].

Conclusions

Currently, there are no established scenarios in AML to proceed to allogeneic HSCT without cytotoxic or targeted therapy. Although lower disease burden or MRD negativity is known to predict improved survival and decreased relapse rates post-HSCT in AML, no such convincing factors have been identified for influencing transplant outcomes in MDS or myelofibrosis. Ongoing studies on microtransplantation may shed further light on the issue of HSCT without disease-directed therapy.

Declaration of competing interest

No disclosures relevant to this topic.

References

[1] Hatzimichael E, Tuthill M. Hematopoietic stem cell transplantation. Stem Cells Cloning 2010;3:105–17.
[2] Appelbaum FR. Hematopoietic cell transplantation for adults with acute myeloid leukemia with minimal residual disease. Best Pract Res Clin Haematol 2015;28:133–40.
[3] Araki D, Wood BL, Othus M, Radich JP, Halpern AB, Zhou Y, et al. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia: time to move toward a minimal residual disease–based definition of complete remission? J Clin Oncol 2016;34. 329-136.
[4] Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol 2017;35:1154–61.
[5] Walter RB, Gyurkocza B, Storer BE, Godwin CD, Pagel JM, Buckley SA, et al. Comparison of minimal residual disease as outcome predictor for AML patients in first complete remission undergoing myeloablative or nonmyeloablative allogeneic hematopoietic cell transplantation. Leukemia 2015;29:137–44.
[6] Lindsley RC, Saber W, Mar BG, Redd R, Wang T, Haagenson MD, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med 2017;376:536–47.
[7] Warlick ED, Cioc A, Defor T, Dolan M, Weisdorf D. Allogeneic stem cell transplantation for adults with myelodysplastic syndromes: importance of pretransplant

disease burden. Biol Blood Marrow Transplant 2009;15:30–8.
[8] Della Porta MG, Alessandrino EP, Bacigalupo A, van Lint MT, Malcovati L, Pascutto C, et al. Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. Blood 2014;123:2333–42.
[9] Nakai K, Kanda Y, Fukuhara S, Sakamaki H, Okamoto S, Kodera Y, et al. Value of chemotherapy before allogeneic hematopoietic stem cell transplantation from an HLA-identical sibling donor for myelodysplastic syndrome. Leukemia 2005;19:396–401.
[10] Field T, Perkins J, Huang Y, Kharfan-Dabaja MA, Alsina M, Ayala E, et al. 5-Azacitidine for myelodysplasia before allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2010;45:255–60.
[11] Gerds AT, Gooley TA, Estey EH, Appelbaum FR, Deeg HJ, Scott BL. Pretransplantation therapy with azacitidine vs induction chemotherapy and post-transplantation outcome in patients with MDS. Biol Blood Marrow Transplant 2012;18:1211–8.
[12] Shanavas M, Popat U, Michaelis LC, Fauble V, McLornan D, Klisovic R, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with myelofibrosis with prior exposure to janus kinase 1/2 inhibitors. Biol Blood Marrow Transplant 2016;22:432–40.
[13] Spitzer TR. Microtransplantation: a new paradigm for the separation of graft versus host disease and graft versus tumor? J Clin Oncol 2012;30:4051–2.
[14] Guo M, Hu KX, Liu GX, Yu CL, Qiao JH, Sun QY, et al. HLA-mismatched stem-cell microtransplantation as postremission therapy for acute myeloid leukemia: long-term follow-up. J Clin Oncol 2012;30:4084–90.
[15] Guo M, Chao NJ, Li J-Y, Rizzieri DA, Sun Q-Y, Mohrbacher A, et al. HLA-mismatched microtransplant in older patients newly diagnosed with acute myeloid leukemia: results from the microtransplantation interest group. JAMA Oncol 2018;4:54–62.