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Autologous hematopoietic cell transplantation for adult acute myeloid leukemia: An obsolete or resurfacing concept?

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A B S T R A C T

Improving long-term outcomes of adult acute myeloid leukemia (AML) patients remains a challenge. Major scientific and clinical advances have led to a better understanding of the disease biology, and the majority of patients achieve a complete remission (CR) after induction therapy. Relapse risk, however, remains considerable and is the leading cause of death in this patient population. Significant efforts to improve outcomes emphasize use of post-remission therapies such as hematopoietic cell transplantation (HCT), an increasingly utilized modality. Improvement in transplantation techniques, understanding of donor:-recipient histocompatibility, and increased availability of alternative donors have resulted in greater use of allogeneic HCT. Despite a graft-versus-leukemia effect and lower post-HCT relapse rates, allogeneic HCT continues to be plagued by treatment-related mortality (TRM) and chronic graft-versus-host disease. Better understanding of AML risk stratification and issues relating to minimal residual disease (MRD) as well as extremely low TRM rates with autografts have prompted clinicians to re-explore use of autologous HCT in subsets of favorable and intermediate-risk CR1 AML patients. Herein, we highlight the evolving literature and treatment outcomes for autologous HCT in AML. We provide recommendations for considering this therapeutic modality for treatment intensification in AML.

1. Introduction

Although the majority of adult acute myeloid leukemia (AML) patients achieve complete remission (CR) with induction chemotherapy, relapse risk remains considerable and is particularly high in older persons and in those with unfavorable cytogenetic and molecular abnormalities [1,2]. Hence, over the past three decades, intense efforts aided by significant scientific and clinical advances, have focused on improving outcomes for patients in first complete remission (CR1) by improving post-remission therapy. The greater experience and understanding in supportive care, histocompatibility and tissue typing advances, recognition of different disease biologic behaviors, improved graft-versus-host disease (GVHD) prophylaxis strategies, and a vast expansion of potential donor sources beyond matched-siblings (including matched unrelated adult donors, umbilical cord blood and haplo-identical donors) have vaulted hematopoietic cell transplantation (HCT) into a commonly

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utilized, life-saving tool [3–5]. Gratwohl and colleagues [6] reported the attainment of the one millionth HCT worldwide and in 2014 in Europe alone, 40,829 HCT procedures were performed, including 3995 for AML patients in CR1 [7].

The type and intensity of post-remission therapy have been the subject of extensive debate. In general, the recommendations for adult AML patients in CR1 are to utilize consolidation chemotherapy in so-called favorable-risk disease and reserve allogeneic HCT for unfavorable-risk disease; there is less agreement on these strategies in intermediate-risk AML in CR1. Autologous HCT had been utilized several decades ago. Due to an unacceptably high early treatment-related mortality (TRM) of 14%, the labor-intensive efforts required in the harvest and in vitro purging of bone marrow, and the reluctance of patients and physicians alike to accept assignment in prospective, randomized studies, this modality has been utilized less frequently [8]. Currently in the USA, autologous HCT is seldom employed (Figs. 1 and 2). Two meta-analyses of a number of trials using autologous HCT in AML CR1 have been reported. Nathan and co-workers [9] analyzed six prospective trials in which bone marrow was the graft source. Although disease-free survival was improved, survival was not better when compared to conventional therapy. Later, Wang and colleagues [10] analyzed newer approaches that now used mobilized blood as the graft source. Similarly, the data showed superior disease-free survival, but not overall survival when compared to chemotherapy. As a result, an evidence-based review by Oliansky et al. [11] concluded that autologous HCT did not provide a significant advantage over chemotherapy.

Subsequently, several investigators have reported very low TRM and excellent outcome data using autologous HCT in AML CR1 [12,13]. These and other experiences again re-open a question that does not appear to go away, that we address herein: Is it time to re-visit autologous transplants for AML?

2. Issues regarding choice of donor graft source

Allogeneic HCT is associated with a high morbidity and TRM secondary to engraftment failure, GVHD, continued need for post-transplant immunosuppression, and high rates of infections. These complications are magnified with greater genetic disparity between the donor and recipient. On the other hand, autologous HCT has the potential advantages of very low TRM, a faster time to transplant for not having to secure an allogeneic donor, no risk of graft rejection, and no risk for GVHD. The obvious drawbacks include higher relapse rates due to lack of the allogeneic, ie, graft-versus-tumor, effect and potential infusion of leukemia cells, and slower hematopoietic reconstitution. Additionally, the post-transplant quality of life is considerably worse after allogeneic transplant when compared to autologous HCT [14,15].

3. Historic perspective

In the late 1970's and early 1980's, investigators first began using autologous HCT for consolidation in AML patients who did not have a suitable HLA-identical sibling donor for allogeneic HCT [16–18]. Bone marrow was used as the source of hematopoietic progenitor cells. Due to concerns of occult tumor in the remission marrow, various strategies to eliminate these cells were developed and termed ‘purging’ techniques. In addition to the significant time and expense of the labor-

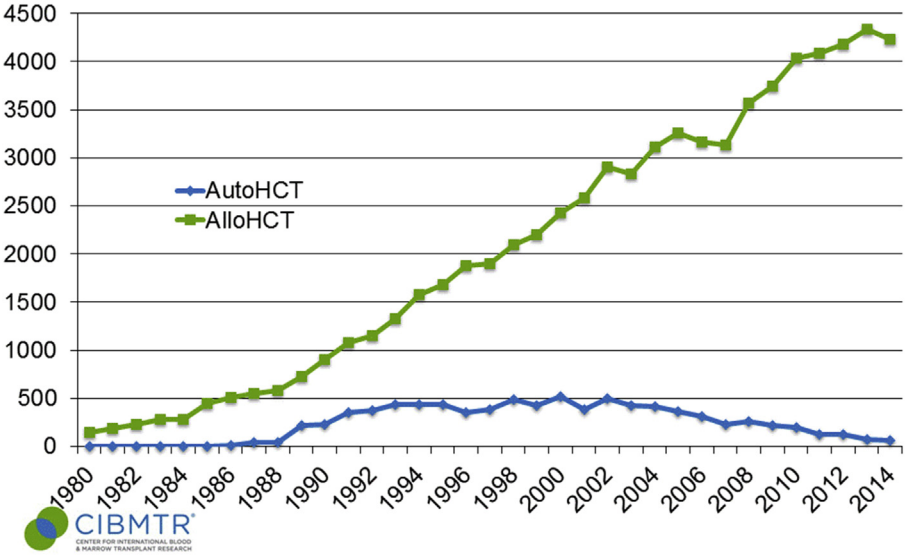

Fig. 1. The number of autologous (autoHCT) versus allogeneic (alloHCT) hematopoietic cell transplants registered to the Center for International Blood and Marrow Transplant Research during the period 1980 to 2014. [D'Souza A, Zhu X. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2015. Available at: http://www.cibmtr.org].

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