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Autologous stem cell transplantation versus alternative allogeneic donor transplants in adult acute leukemias

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ABSTRACT

The availability of alternative sources of stem cells including most recently T-replete haploidentical marrow or peripheral blood, and the increasing use of reduced-intensity conditioning (RIC), renders feasible an allogeneic transplant to almost all patients with acute leukemia up to 70 years of age. Autologous stem cell transplantation (ASCT) for consolidation of complete remission (CR), however, offers in some circumstances an alternative option. Although associated with a higher relapse rate, autologous transplant benefits from a lower non-relapse mortality, the absence of graft-versus-host disease (GVHD), and a better quality of life for long-term survivors. The recent use of intravenous busulfan (IVBU) with high-dose melphalan, better monitoring of minimal residual disease (MRD), and maintenance therapy post autografting bring new interest. Few retrospective studies compared the outcome following alternative donor versus autologous transplants for remission consolidation. Genoidentical and phenoidentical allogeneic stem cell transplantations are undisputed gold standards, but there are no data showing the superiority of alternative allogeneic donor over autologous transplantation, at the time of undetectable MRD, in patients with good- and intermediate-1 risk acute myelocytic leukemia (AML) in first complete remission (CR1), acute promyelocytic leukemia in second complete remission (CR2), and Philadelphia chromosome–positive (Ph^+) acute lymphocytic leukemia (ALL).

1. Introduction

In the past 20 years, considerable development has occurred in the field of allogeneic stem cell transplantation. While in the early days only 25% of all patients with acute leukemia younger than 35 years of age could, if needed, be transplanted using exclusively a human leukocyte antigen (HLA) identical sibling, now almost all adult patients in need of a transplant up to 70 years of age may have a donor, due to the introduction of reduced intensity conditioning (RIC), on the one hand, and the availability of alternative stem cell sources on the other hand [1]. Alternative sources have successively included unrelated matched 10/10 or 8/8 and even 9/10 mismatched volunteer donors, cord blood (single or double), and most recently T-replete haploidentical donors. Several measures have rendered T-replete haploidentical transplants feasible [2], including the use of granulocyte colony-stimulating factor (G-CSF) primed marrow [2], the combination of primed marrow and peripheral blood stem cells [3,4], and, probably the most instrumental one, the use of high-dose cyclophosphamide (CY) to prevent graft-versus-host disease (GVHD) [5–10]. The present results using high-dose CY have shown a considerable reduction in incidence and severity of acute and chronic GVHD to such an extent that high-dose CY is being considered for prevention of GVHD with the other alternative stem cell sources and possibly even identical sibling transplants.

The use of autologous stem cell transplantation (ASCT) as consolidation therapy for adult patients with acute leukemia has declined over time as allogeneic transplantation has become available for almost all patients. Nevertheless, the registry of the European Society for Blood and Marrow Transplantation (EBMT) contains data on 27,000 patients who received autografts for acute leukemias and an estimated 50,000 patients throughout the world have been autografted for consolidation of acute leukemia. Fig. 1 shows the evolution of ASCT practice for consolidation of complete remission (CR) in adult patients with acute leukemia over time as evaluated through the EBMT registry; for many teams ASCT remains a therapeutic option, taking into account that multiple randomized studies, including very recent ones, have reported lower relapse rates after ASCT compared with chemotherapy [11–13] as well as lower non-relapse mortality (NRM) rates compared with allogeneic transplantation. In addition, quality of life of long-term survivors is better after ASCT than after allogeneic transplantation [14]. Recent developments also have occurred in

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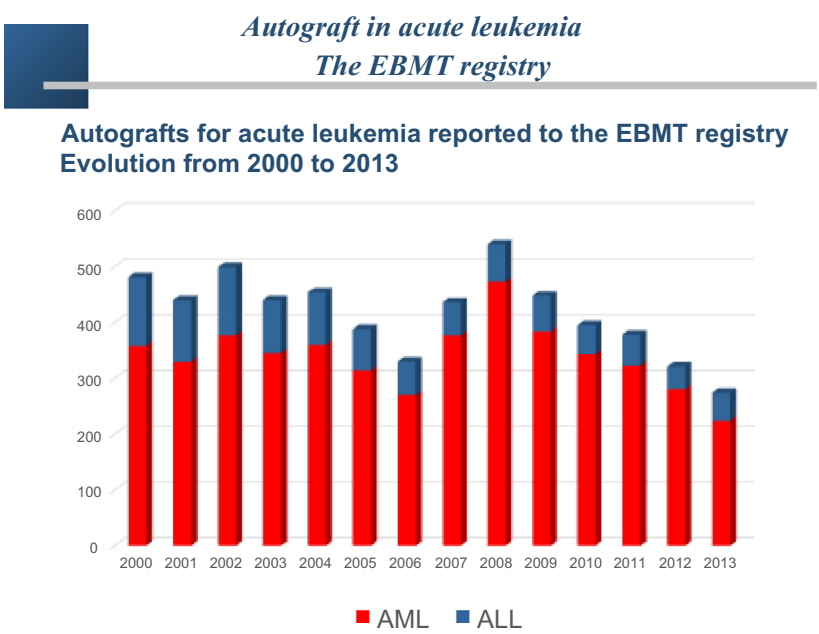

Fig. 1. Evolution over time of ASCT for consolidation of complete remission in adult patients with acute leukemia (EBMT source).

the field of ASCT improving outcomes. These include the use of intravenous busulfan (IVBU), which reduces toxicity [15], and the combination of IVBU with high-dose melphalan (HDM), which reduces the relapse incidence (RI), better detection of minimal residual disease (MRD) with molecular biology techniques, and the introduction of post-transplant maintenance therapy. A recent review on ASCT in acute leukemia [16] has proposed that good- and intermediate-1 risk acute myelocytic leukemia (AML) patients in first complete remission (CR1), patients with acute promyelocytic leukemia in second complete remission (CR2), patients with Philadelphia chromosome–positive (Ph^+) acute lymphocytic leukemia (ALL), and more widely, all adult patients with MRD-negative status be considered for ASCT.

In this context, while a genoidentical transplant remains the gold standard, and a matched unrelated donor in its absence is favored by most teams, the question whether a mismatched allogeneic transplant should be preferred to an ASCT is unsolved and important. The existing data comparing unrelated, cord blood and haploidentical transplants to ASCT in adult acute leukemia are unfortunately limited and only retrospective. It is the purpose of this chapter to review them. However, recent development of ASCT for acute leukemias should first be taken into account.

2. Autologous stem cell transplantation: recent data and present guidelines

We will only briefly summarize here historical results, recent improvements and updated proposed guidelines.

2.1. Historical results

2.1.1. In AML

Two important meta-analyses of several randomized studies and retrospective studies from the EBMT [17,18] and the Center for International Blood and Marrow Transplantation Research [19] (CIBMTR), have reported a long-term leukemia-free survival (LFS) of approximately 50% for AML patients who underwent ASCT in CR1 and approximately 30% in CR2. A prospective, randomized phase III trial recently carried out by the Dutch–Belgian (HOVON) and Swiss Group (SAKK) [11,13] compared ASCT with intensive consolidation chemotherapy in AML patients in CR1. Patients who underwent ASCT showed a markedly reduced RI and had increased LFS at 5 years. The CIBMTR [19] concluded that, in the absence of a matched sibling donor, ASCT may be an acceptable post-remission therapy in CR1.

Recent developments aim at improving these results (see below).

2.1.2. In ALL

The use of ASCT in adults has remained controversial. In the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 [20] study, overall survival (OS) was significantly worse in the ASCT group compared to chemotherapy. A recent randomized study of 433 adult standard-risk ALL patients showed that LFS at 5 years was significantly better in patients who underwent allogeneic transplantation compared with ASCT [21]. A meta-analysis using data from 13 studies including 2,962 patients [22], excluding Ph^+ patients, showed no beneficial effect of ASCT compared with chemotherapy. In contrast, some more recent studies favored ASCT: in a limited unicentric series [23] of 79 adolescents with ALL who received a "total therapy protocol" based on ASCT in CR1 from 1990 to 2009, OS and LFS at 5 years were 63% and 62%. Time to CR >4 weeks was the only unfavorable prognostic factor by multivariate analysis. Regarding patients older than 55 years, a recent retrospective EBMT study [24] evaluated 267 patients who underwent RIC allogeneic hematopoietic stem cell transplant (allo-HSCT) and 179 patients who underwent ASCT in CR1. The 2-year OS was 44% for RIC–allo-HSCT and 57% for ASCT ($P = .02$), and LFS rates were 34% and 41%, respectively ($P = .06$). In Ph^+ BCR/ABL-positive patients, accumulating evidence have suggested good outcomes after ASCT in MRD-negative patients treated with tyrosine kinase inhibitors (TKIs) [25].

2.2. Recent improvements

Recent developments have occurred in pretransplant conditioning, as well as better monitoring of MRD and the possible introduction of maintenance therapy post ASCT.