

Autologous Stem Cell Transplantation in AML

Norbert Claude Gorin, Myriam Labopin, Emmanuelle Polge, Vanderson Rocha

Department of Haematology and Oncology and EBMT Data Management Office, Hopital Saint-Antoine APHP and Université Pierre et Marie Curie, Paris, France

Autologous hematopoietic stem cell transplantation remains presently an interesting therapeutic option in adult patients with AML beyond 35 years of age or if younger with no identical sibling for an allogeneic transplantation.

Data from the EBMT registry indicate on a total of 1714 patients autografted after 1995 in first remission (CR1) a leukaemia free survival (LFS) at 5 years of $46 \pm 2\%$ highly reproducible and indeed identical when comparing Eastern Europe country data to other European countries. Several randomized studies, although not all, comparing allogeneic transplants in patients with HLA matched siblings to autologous bone marrow transplantation and to conventional chemotherapy, have shown the superiority of the allogeneic transplant approach (when feasible) to the other approaches, but also the superiority of autografting over conventional chemotherapy. None has ever shown the superiority of conventional chemotherapy. However, when reanalyzed by cytogenetics the US intergroup and the British MRC studies have shown in fact the superiority of allogeneic transplants in poor risk patients, and the superiority of ASCT in good risk patients.

The EBMT has recently investigated the outcome of patients with AML who could be defined as good risk either by clinical criteria (age <35 years and complete remission achieved within 40 days) or by cytogenetics (core binding factor mutations, inv 16 and t(8;21)) submitted to ASCT:

1) 458 adult patients with clinical good risk criteria autografted in CR1 were compared to 2218

patients classified as non good risk: the LFS was $56 \pm 2\%$ versus $38 \pm 1\%$. The relapse rate was $40 \pm 2\%$ versus $55 \pm 1\%$.

2) 383 patients in the EBMT registry, with inv 16 or t(8;21) were transplanted after 1990, 158 autografted and 140 allografted in CR1. Allografted recipients were younger (34 years versus 41, $p < 10^{-4}$) and received their transplant earlier (Interval from diagnosis to transplant: 137 versus 161 days, $p < 10^{-4}$). In addition the allograft procedure used more marrow as a stem cell source (69% vs 28%, $p < 10^{-4}$) and total body irradiation (60% versus 26%, $p < 10^{-4}$) rather than myeloablative chemotherapy in the conditioning. In CR2, 32 patients were autografted and 52 allografted.

Interestingly in CR1 LFS was similar following both transplant procedures (allografts: $61 \pm 5\%$, autografts $56 \pm 5\%$ at 10 years). In contrast in CR2 allografting resulted in superior outcome (LFS : $58 \pm 7\%$ versus $30 \pm 11\%$).

The non relapse mortality following the autograft procedure was only $5 \pm 4\%$ in CR1, but $17 \pm 11\%$ in CR2.

For patients in CR1, the median age of the population was 37 years. In those below 37 years, the LFS following allo and autografting were respectively $73 \pm 6\%$ and $58 \pm 7\%$. In those above 37 years the results were $52 \pm 7\%$ and $60 \pm 7\%$ suggesting that autografting may be safer in older patients with core binding factor mutations.

Recent studies from the Pethema group and from UCSF confirm these findings. In the Pethema LMA 99 protocol, the LFS following ASCT in adult AML was 53% at 4 years, but in fact around 60% in patients with good and intermediate groups versus 23% only in patients of the poor risk category. In UCSF 9302 protocol, the DFS for all patients was 52% at 12 years, but in fact 68% in patients with favorable cytogenetics, 48% in patients of the intermediate risk category and 10% only in the poor risk category.

These data highlight the fact that ASCT in AML is most likely to benefit, as in other malignant blood diseases (lymphomas in particular) to patients with good prognostic criteria including high chemosensitivity. There is a need in this good risk patient population to launch randomized studies comparing conventional chemotherapy including high dose ARA-C to ASCT.

These results also are consistent with the recent EBMT analysis of 625 patients with acute promyelocytic leukaemia (APL M3) transplanted with auto- or allogeneic-HSCT after 1993. Estimated 5 years-leukemia free survival for patients transplanted in CR1 was 69% for 149 patients autografted and it was 68% for 144 patients allografted. However the reasons why these patients in CR1 were transplanted remain unclear in the ATRA era.

For transplants in CR2, 5-y LFS was 47% in 195 autoHSCT and 59% in 137 alloHSCT recipients, respectively. ASCT is an important therapeutic tool in patients with M3 AML achieving molecular CR2.

An important question is whether adult patients with AML and no family matched donor should go to ASCT or to unrelated transplants. The Center for International Blood and Marrow Transplant Research has recently compared ASCT to unrelated donor allotransplants: they studied the outcomes of 668 autotransplants compared with 476 URD transplants. Proportional hazards regression adjusted for differences in prognostic variables. In multivariate analyses, transplant-related mortality (TRM) was significantly higher and relapse lower with URD transplantation. Adjusted 3-year survival probabilities were: in CR1 57 (53-61)% with autotransplants and 44 (37-51)% with URD ($P = 0.002$), in CR2 46 (39-53)% and 33 (28-38)% respectively ($P = 0.006$). Adjusted 3-year leukaemia-free survival (LFS) probabilities were: CR1 53 (48-57)% with autotransplants and 43 (36-50)% with URD ($P = 0.021$), CR2 39

(32-46)% and 33 (27-38)% respectively ($P = 0.169$). Both autologous and URD transplantation produced prolonged LFS. High TRM offsetted the superior antileukaemia effect of URD transplantation. The conclusion was that this retrospective, observational database study showed that autotransplantation, in general, offered higher 3-year survival for AML patients in CR1 and CR2. Cytogenetics, however, were known in only two-thirds of patients and treatment bias could not be eliminated.

The recent introduction of non myeloablative transplants with a reduction of TRM has reinitiated the debate and rendered the decision tree more difficult to build. The EBMT registry has compared retrospectively the outcome of 204 HLA-identical sibling RIC allo transplants (RIC) versus 954 auto transplants done from 1997 to 2003 in patients over 50 years of age. For RIC 87% of the non myeloablative regimens were built around fludarabine. For ASCT, the conditioning contained Total Body Irradiation (TBI) in 35% of the cases. In RIC patients the incidence of acute graft versus host disease (GVHD) score III-IV was only 9% but the cumulative incidence of chronic GVHD at 1 year was $46 \pm 4\%$ (50% extensive). The non relapse mortality at 2 years was $20 \pm 3\%$ following RIC versus $11 \pm 1\%$ following ASCT. The relapse incidence was higher following ASCT in CR1 than following RIC ($37 \pm 5\%$ versus $25 \pm 3\%$, $p = 0.03$). The LFS in patients transplanted in CR1 were superposable at 2 years ($43 \pm 2\%$ following ASCT, $41 \pm 6\%$ following RIC). The quality of life was likely better following ASCT in the absence of chronic GVHD. In CR2 result were better following RIC transplants: $57 \pm 9\%$ versus $26 \pm 6\%$ only following ASCT.

The question whether purging the graft in vitro improves the outcome is no longer addressed although several studies in the nineties have shown its efficacy. Part of the reason has been the long duration of aplasia following autografting with marrow treated in vitro with cyclophosphamide derivatives. Recent studies have focussed on purging peripheral blood hemopoietic stem cells with mafosfamide, and on expansion in vitro of grafts purged by mafosfamide: these studies have produced preliminary data showing that rapid engraftment can be obtained following the use of mafosfamide. In parallel, new agents for in vitro purging, that spare normal counterparts, such as TDZD-8 (4-Benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione) are being studied..

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