Outcome of Allografting for AML-CR2 is equivalent across the BSBMT and EBMT and is associated with encouraging OS and DFS across all age groups.

Jenny Byrne[1,2], Rachel Pearce[2], Julia Perry[2], C Crawley[3.2], Graham Jackson[4,2]

Affiliations:

[1]Nottingham University Hospitals Trust, Nottingham, UK

[2]British Society for Blood and Marrow Transplantation, Guys and St Thomas Hospital, London, UK

[3] Addenbrookes Hospital Trust, Cambridge, UK

[4] Newcastle Royal Infirmary Trust, Newcastle, UK

Corresponding author:

Dr Jenny Byrne

Department of Haematology

Nottingham University Hospitals Trust

Hucknall Road, Nottingham NG5 1PB

None of the authors have any Conflicts of Interest to declare.

Running Title: *Outcomes of allografting for AML-CR2…*

Allogeneic HSCT is the most effective anti-leukaemic therapy for AML. However, due to the significant risks of transplant-related mortality (TRM) from infection, regimen-related toxicities and graft versus host disease (GVHD), not all patients receive transplants in CR1. Currently this decision depends on risk stratification, balancing the risks of relapse versus TRM. In general, allogeneic transplantation is reserved for intermediate or poor risk patients in CR1, but not good risk patients who have a lower chance of relapse and a high chance of salvage[1,2]. Following relapse, AML has a poor outlook[3]. The only curative approach is with an allogeneic transplant following re-induction chemotherapy, where superior outcomes have been confirmed as compared to those not transplanted[4,5]. It is often perceived that allografts for AML-CR2 have inferior outcomes as compared to CR1 transplants, but there is limited published data for those allografted in CR2 since most studies report data for CR1 and CR2 patients combined.

We analysed the outcomes of 534 UK and 3070 AML-CR2 patients reported to the EBMT, from 2006-11. There was a 50% increase in the number of AML-CR2 allografts performed during this time-period in both BSBMT (70 to 104) and EBMT (420 to 623) cohorts. RIC conditioning regimens exceeded myeloablative regimens, accounting for 55% and 66% of transplants done by the BSBMT and the whole cohort. Furthermore, 19% of UK allografts for AML-CR2 and 16% of the EBMT cases were in patients aged > 60 years. The proportion of paediatric cases was similar (14% and 15%) in the two cohorts. Greater than 60-75% of the allografts were performed using an unrelated donor and the source of stem cells was PBSC in > 70% of cases, with 10% or fewer being from cord blood. Although the length of CR1 was largely unknown, the median time from AML diagnosis to transplant was 18-19 months in both groups suggesting an average CR1 duration of 6-12 months.

The median follow up for the BSBMT cohort was 4.75 years and 3.3 years for the EBMT. Overall survival (OS) at 3 and 5 years for the BSBMT group was 49% and 44% and for the EBMT was 53% and 48% respectively (p=ns). Similarly, there was no difference between the BSBMT and the EBMT

cohorts in LFS rates, TRM rates, or relapse rates at 1, 3 or 5 years. Most relapses occurred early with 23% and 21% at 1 year in the BSBMT and EBMT groups rising to 29% and 30% at 3 years. The D100 TRM rates were low at 9% and 10% for the UK and EBMT cohorts, rising to 29% and 27% at 5 years. The incidence of both acute (50% versus 48%) and chronic GVHD (49% versus 35%) were similar between the two groups.

Multivariate analysis of factors influencing OS revealed age and time from diagnosis to transplant to be significant. The impact of age was striking with paediatric patients aged < 18 years having the best OS of 58% at 3 years as compared to 52% for those aged 18-60 years and 45% for those aged > 60 years. Relapse was significantly higher in those receiving RIC versus MAC conditioning, who had no acute GVHD and a shorter time from diagnosis to transplant. Similarly, LFS was influenced by time from diagnosis to transplant and type of conditioning, whilst age, source of stem cells, presence of acute GVHD and time from diagnosis to transplant influenced TRM (Figure).

Allogeneic transplants for AML-CR2 represent an important part of any allograft program. Ever since cytogenetic risk groups were characterised, most patients with monosomal/adverse risk karyotypes have been transplanted in CR1 and thus those allografted in CR2 represent a distinct group, comprising patients with intermediate/good risk cytogenetic profiles. In this study, cytogenetic data was incomplete and so could not be analysed for its impact on outcomes. More recently, AML risk stratification has included molecular analysis, but at the time of this study few patients had molecular profiles recorded.

The factors impacting OS, relapse and TRM were all expected. The best results were observed in patients aged < 18 years who had a 3 year OS of 58%. The negative effect of increasing age on OS and TRM has long been recognised and there was a clear inferior survival for those aged > 60 years compared to those aged 18-60 years[6,7]. Furthermore the higher TRM rates and reduced OS seen with the use peripheral blood or cord blood was expected given the known increased risk of GVHD following PBSC transplants[8] and the increased risk of graft failure and NRM following cord blood

transplantation[9]. Similarly, the increased relapse risk in patients undergoing RIC transplants, those with shorter CR1 duration and no acute GVHD are well known, as is the increased TRM in patients developing acute GVHD. It is encouraging that no major differences were observed between the BSBMT and EBMT cohorts in this benchmarking study confirming that outcomes are comparable across Europe for AML-CR2 patients.

The increasing number of AML-CR2 allografts during this time-period may reflect the increasing use of risk stratification algorithms in AML, which select out only high risk patients for allografting in CR1. For such strategies to be justifiable it is important that transplant outcomes in CR-2 is comparable to that in CR1. It is encouraging that the 5 year OS of 44% and 48% in the BSBMT and EBMT cohorts is comparable with other studies which have reported 50% and 42% 5 year OS for AML-CR2[5,10,]. In addition, these outcomes are reasonable compared to those reported for adult patients in CR1, where 3 year OS of 51% and 5 year OS of 54% have been reported[11], thus supporting the concept of reserving allografts for poor risk patients in CR1.

Another reason for the increased CR2 allografts may be that more patients are eligible due to more successful re-induction regimens, or the introduction of RIC regimens, which enable older and less fit patients to undergo transplantation. Indeed, 16% of our patients were aged > 60 years and their OS was 45% at 3 years, which questions previous studies that have suggested that allogeneic transplantation in patients > 60 years be limited to those in CR1[12]. The superior results observed for older patients in CR2 may reflect better patient selection and lower HCT-CI scores, although this cannot be proven as comorbidity scores were unavailable.

In summary, this large registry study confirms acceptable outcomes for AML-CR2 allografts in all age groups and supports risk stratification and reservation of allo-transplantation in CR1 for high risk patients. It is likely that risk stratification models will continue to evolve as new molecular prognostic data and MRD information is included and thus patient selection will be further refined.

References

1. Cornelissen J, Gratwohl A, Schlenk R, Sierra J, Bornhauser M, Juliusson G *et al.* The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol* 2012; **9** : 579-590
2. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T *et al.* Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017; **129** :424-447
3. Forman SJ and Rowe JM. The myth of the second remission of acute leukaemia in the adult. *Blood* 2013; **121**:1077-1082
4. Gale R, Horovitz M, Rees JK, Gray RG, Oken M, Estey EY *et al.* Chemotherapy versus transplantation for acute myelogenous leukemia in second remission. *Leukemia* 1996*;* **10***:* 13-19
5. Burnett AK, Goldstone A, Hills RK, Milligan D, Prentice A, Yin J *et al*. Curability of patients with acute myeloid leukaemia who did not undergo transplantation in first remission*. J Clin Onc* 2013; **31**: 1293-1301
6. Michelis FV, Atenafu EG, Gupta V, Kim D, Kuruvilla J, Lambie A *et al.* Duration of first remission, haemopoietic cell transplantation-specific comorbidity index and patient age predict survival of patients with AML transplanted in second CR. *Bone Marrow transplant* 2013; **48:** 1450-1455

7. Michelis FV, Messner HA, Atenafu EG, McGillis L, Lambie A, Uhm J *et al*. Patient age, remission status and HCT-CI in a combined score are prognostic for patients with AML undergoing allogeneic hematopoietic cell transplantation in CR1 and CR2. *Bone Marrow Transplant* 2015; **50:** 1405-1410
8. Holtick U, Albrecht M, Chemnitz JM, Theurich S, Skoetz N, Scheid C *et al.* Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation for haematological malignancies in adults (Review) *Cochrane Database of System Rev* 2014 Apr 20;(4):CD010189
9. Eapen M, Rocha V, Sanz G, Scaradavou A, Zhang MJ, Arcese W *et al.* Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. *Lancet Oncol* 2010; **11:** 653-70
10. Weisdorf DJ, Millar HR, Horowitz MM, Hyare PS, Champlin R, Ho V *et al*. Allogeneic transplantation for advanced acute myeloid leukemia: the value of complete remission. *Cancer* 2017; **123:** 2025-2032
11. Koreth J, Schlenk R, Kopecky K, Honda S, Sierra J, Djulbegovic B *et al.* Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: a systematic review and meta-analysis of prospective clinical trials. *JAMA* 2009; **301**: 2349-2361
12. Michelis FV, Messner HA, Atenafu EG, Kim DD, Kuruvilla J, Lipton JH *et al*. Benefit of allogeneic transplantation in patients age > 60 years with acute myeloid leukaemia is limited to those in first complete remission at time of transplant. *Biol BMT* 2014; **20**; 474-479

Figure Legends

Figure 1

Survival curves

a) Overall survival of AML-CR2 allografts, BSBMT versus EBMT

b) Leukaemia-free survival of AML-CR2 allografts, BSBMT versus EBMT

c) Overall survival of whole group by age (< 18 yrs, 18-60 years and > 60 years)

d) Leukaemia free survival of whole group by time from diagnosis to transplant (< 18 months compared to > 18 months)

e) Non-relapse mortality of whole group by stem cell source (bone marrow versus PBSC versus cord blood)

f) Relapse rate of whole group by type of conditioning (RIC versus MAC)