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Blood 142 (2023) 425–427

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

The Benefit of Allogeneic Transplant in 1 st Complete Remission in *NPM1* Mutated AML with or without *FLT3* ITD Is Restricted to Those Testing MRD Positive after Induction - an Analysis of the UK NCRI AML17 and AML19 Studies

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Background

While there is accumulating evidence that measurable residual disease (MRD) negative patients with intermediate risk AML may not benefit from allogeneic transplantation in 1 st complete remission (CR1-allo), many consider the presence of a *FLT3* Internal Tandem Duplication (ITD) an indication for this procedure. However, the studies supporting this practice were mainly performed before the development of sensitive molecular MRD techniques (Schlenk *NEJM* 2008).The UK NCRI AML17 and AML19 trials studied, then incorporated, MRD by RT-qPCR into the management of patients with *NPM1* mutated AML.

Methods

NCRI AML17 (April 2009 to December 2014) and AML19 (November 2015 to November 2020) were sequential prospective randomised trials for younger adults (18 - 60 years) with newly diagnosed AML. In AML17, decisions regarding CR1-allo were made using a validated risk score incorporating baseline factors and response to induction. In AML19, for patients with *NPM1* mutated AML (*NPM1* ^{mut}) the protocol recommended CR1-allo only in patients testing MRD positive in the peripheral blood (PB) post cycle 2 (PC2), regardless of other baseline risk factors such as *FLT3* ITD, based on findings from AML17 (Ivey *et al*, NEJM 2016). Both trials were performed prior to the availability of midostaurin and *FLT3* ITD MRD assays. Here we compare the outcomes of patients with *NPM1* ^{mut} in these trials and assess the benefit of CR1-allo according to *FLT3* ITD and molecular MRD status. Time-to-event variables are analysed using the Kaplan-Meier method, and the impact of alloSCT assessed using time-dependent Cox regression and visualised with Simon-Makuch plots. Molecular relapses were included as relapse events, and alloSCT performed after molecular relapse was not considered as CR1.

Results

737 patients with *NPM1* ^{mut}AML who achieved CR/CRi and had a valid PC2 PB MRD result were included in the analysis. 60/348 (17%) patients from AML17 and 83/389 (21%) from AML19 tested PB PC2 MRD positive. Overall, CR1-allo was performed in 20% of patients in AML17 and 25% in AML19. Of the MRD positive patients CR1-allo was performed in 16/60 (27%) in AML17

compared to 50/83 (60%) in AML19 where these patients were recommended for transplant. CR1-allo was performed in 18% and 16% of MRD negative patients in AML17 and AML19 respectively.

In AML17, as previously reported (Ivey *et al*, NEJM 2016), patients who were MRD+ had poor outcomes, with 3-year cumulative incidence of relapse (CIR) of 84% and overall survival (OS) of 25%. These outcomes were improved in AML19, with 3y CIR 50% and 3y OS 51%. Across both trials, CR1-allo was associated with a significant survival benefit in MRD+ patients (3y OS 61% vs 24%, HR 0.42, 95%CI 0.26-0.69, p<0.001, Figure A). Patients who were MRD negative had excellent outcomes in both trials (3y CIR 33% and 24% and 3y OS 75% and 83% for AML17 and AML19 respectively). AlloSCT in CR1 provided no survival advantage for MRD- patients (HR 0.83, 95%CI 0.51-1.34, p=0.4).

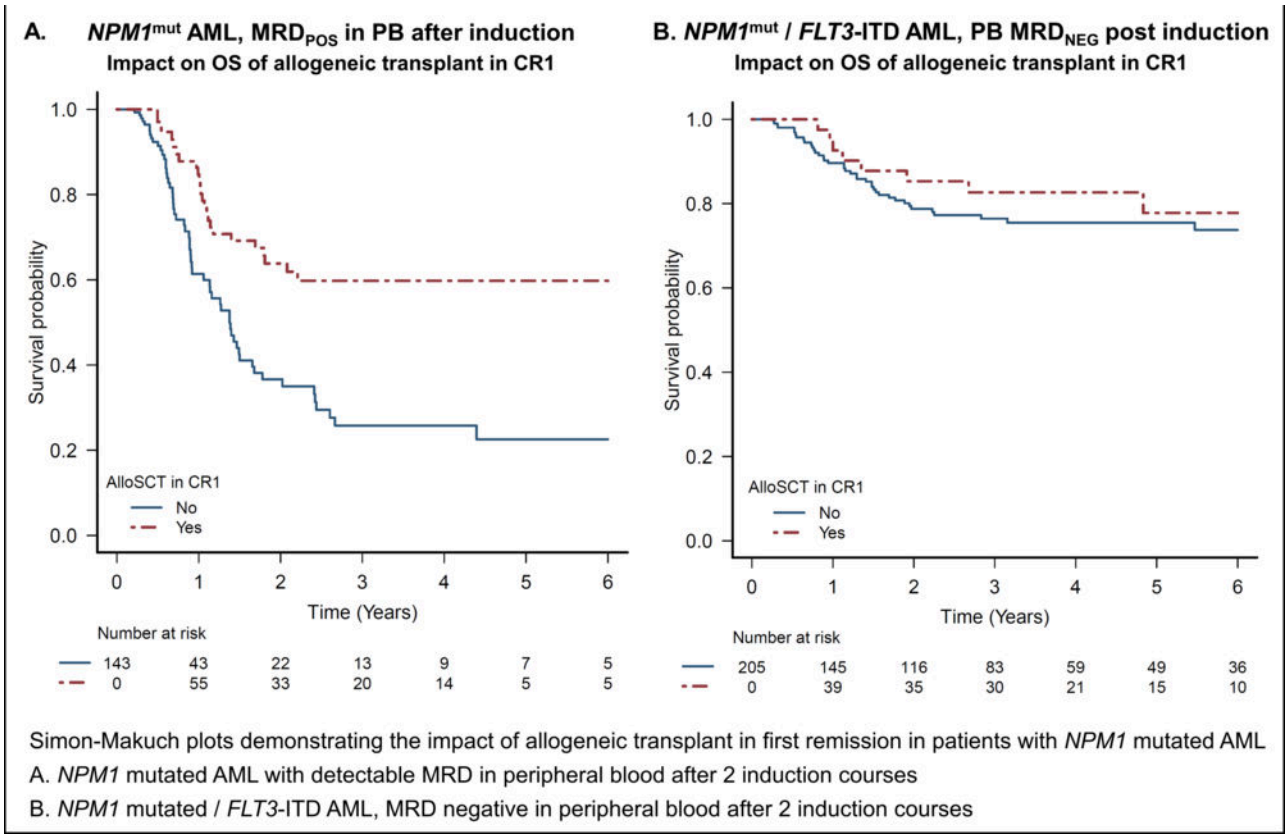
There were a total of 286 patients with *NPM1* ^{mut} *FLT3* ITD ^{mut} AML with a PC2 PB MRD result across both trials. 81/286 (28%) were PB PC2 MRD+ of whom 32/81 (40%) received CR1-allo (28% in AML17 and 49% in AML19). Outcomes in these high-risk patients were improved in AML19, with 3y CIR 91% vs 68% and 3y OS 22% and 31% for AML17 and AML19 respectively. Those who received CR1-allo had improved outcomes (3y OS 45% vs 18%, HR 0.52, 95% CI 0.29-0.93, p=0.03) consistent with the overall MRD+ population.

In the 70% of *NPM1* ^{mut} *FLT3* ITD ^{mut} AML patients who achieved PB PC2 MRD-, outcomes were encouraging in both AML17 (3y CIR 37%, 3y OS 75%) and AML19 (3y CIR 27%, 3y OS 80%). CR1-allo was performed in 20% (19% in AML17, 21% in AML19), with no survival benefit for transplant (HR 0.80, 95% CI 0.37-1.72, p=0.6, Figure B). There remained no benefit when restricted to those with high (>0.5) *FLT3* ITD allelic ratio (HR 0.63, 95% CI 0.2 - 2.23, p = 0.50) and there was also no evidence of an interaction between allelic ratio and benefit from transplant for MRD negative patients (p=0.86).

Conclusion

Molecular MRD can be used to stratify decision making concerning post remission therapy in patients with *NPM1* ^{mut} AML. Patients who achieve MRD negativity in the peripheral blood by the end of course 2 are at low risk of relapse and we found no evidence of benefit from allogeneic transplant in CR1, including in the subset with *FLT3* ITD. This finding contrasts with MRD+ patients where there was a significant survival benefit for CR1 transplant.

Disclosures Freeman: *JAZZ:* Research Funding, Speakers Bureau; *BMS:* Research Funding; *MPAACT:* Membership on an entity's Board of Directors or advisory committees; *NOVARTIS:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Dillon:** *Astellas:* Consultancy, Honoraria, Speakers Bureau; *AvenCell:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Jazz:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Speakers Bureau; *Pfizer:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Shattuck labs:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Research Funding; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau. **Russell:** *Astellas:* Honoraria; *Servier:* Honoraria; *Jazz Pharma:* Research Funding; *Pfizer:* Honoraria, Research Funding, Speakers Bureau.



Simon-Makuch plots demonstrating the impact of allogeneic transplant in first remission in patients with *NPM1* mutated AML

A. *NPM1* mutated AML with detectable MRD in peripheral blood after 2 induction courses

B. *NPM1* mutated / *FLT3*-ITD AML, MRD negative in peripheral blood after 2 induction courses

Figure 1

https://doi.org/10.1182/blood-2023-179033