All patients with acute myeloid leukemia and *FLT3*-ITD should be transplanted in first remission. Also in the era of tyrosine kinase inhibitors? – the CON

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"*The worst form of inequality is to try to make unequal things equal.*" – Aristotle

Allogeneic stem cell transplantation (alloSCT) is an important curative treatment option for a significant proportion of patients with acute myeloid leukemia (AML) although it is well recognized that a subset of patients achieve long-term remission without transplantation.[1] Importantly, alloSCT entails a not insignificant risk of non-relapse mortality due to complications related to the procedure. Therefore, careful evaluation between risk of disease relapse and non-relapse mortality is needed for the challenging decision of whom to transplant in first complete remission (CR1).[2] In this respect there is increasing interest in using measurable residual disease (MRD) analysis after induction to help refine decision-making around post-remission treatment between allogeneic transplant or chemotherapy consolidation. For this purpose highly sensitive MRD assays are required to identify patients with a lower risk of relapse who could avoid the higher non-relapse mortality associated with alloSCT and be cured with intensive chemotherapy alone. This is particularly relevant for patients with European LeukemiaNet (ELN) intermediate-risk disease for whom decisions are more nuanced than for patients with adverse-risk disease for whom transplant is recommended.[1,3] Another important consideration is the effectiveness of salvage therapy and transplantation for relapsed patients not transplanted in CR1. It has become generally accepted that a transplant is indicated when the estimated relapse risk without a transplant is >40%, although more effective salvage options using targeted therapies at molecular relapse might change this calculation.[3] Consequently, we argue that not all patients with *FLT3*-ITD-mutated AML benefit from CR1-alloSCT in the era of high sensitivity MRD testing and with the availability of *FLT3* inhibitors in frontline treatment and at relapse.

Mutations of the FMS-like tyrosine kinase 3 (*FLT3*) gene occur in approximately 30% of all cases of AML, with the internal tandem duplication (ITD) representing the most common type of *FLT3* mutation present in 25% of cases.[4,5] *FLT3*-ITD-mutated (*FLT3*-ITD$^+$) AML is associated with poorer outcomes, with higher relapse rates and reduced overall survival.[6-9] Consequently many centers have considered the presence of a baseline *FLT3*-ITD an indication for transplant in CR1, although there is considerable variation in both recipient selection and transplant strategies.[2] Importantly *FLT3*-ITD$^+$ AML is not one disease, with the mutation frequently co-occurring with other cytogenetic and molecular aberrations.[4,5] Although a *FLT3*-ITD typically confers ELN intermediate risk, smaller proportions of patients are assigned as favorable risk or adverse risk, depending on other genomic lesions detected at diagnosis.[1,5] Thus, in the UK NCRI AML19 clinical trial, which was predominately for younger AML patients <60 years, the most frequently co-mutated gene was *NPM1* which was detected in 55% of cases. In 3% of cases core-binding factor (CBF) gene fusions were present. Adverse co-mutated genetic lesions included *DEK*:*NUP214* (2%), UBTF-tandem duplications (6%), *KMT2A*-partial tandem duplications (9%), and *MECOM* (1%) and *KMT2A* (2%) rearranged case (Figure 1, *unpublished data*). Overall, the *FLT3*-ITD-mutated cohort was divided into ELN 2022 favorable risk (4%), intermediate risk (90%) and adverse risk (6%). These findings highlight the disparity of clinical outcomes in *FLT3*-ITD-mutated AML and have implications for the optimal treatment choice, including the decision to allograft.

For patients with *NPM1* mutations, early retrospective studies indicated that alloSCT improved overall survival for patients with coexisting *FLT3*-ITD, in particular those with an allelic ratio >0.5.[10,11] These studies were performed before the development of sensitive molecular MRD techniques, which have been shown to be strong predictors of relapse and survival in *NPM1*^{mut} AML with or without *FLT3*-ITD.[12-14] Analyzing data from the UK NCRI AML17 trial, Ivey *et al.*[14] re-

ported that patients who were *NPM1*^{mut}/*FLT3*-ITD^{+} and *NPM1* MRD negative (MRD^{-}) by reverse transcriptase quantitative polymerase chain reaction in the peripheral blood (PB) after two courses of chemotherapy had a cumulative incidence of relapse of 35% at 5 years compared to 92% in patients testing MRD positive (MRD^{+}). The suggestion was that MRD assessment could be used to stratify post-induction treatment decisions regarding whether to transplant or not. Patients who are PB MRD^{-} for *NPM1*, who had a favorable survival of 76% at 5 years, may not benefit from a transplant in CR1. Similar results were reported by Cocciardie *et al.*[15] from the AMLSG 09-09 trials: there was no benefit from alloSCT in CR1 in patients who were in molecular remission following the second chemotherapy course. To address this question more comprehensively, Othman *et al.*[16] used data from two prospective, randomized, multicenter UK NCRI clinical trials of intensive chemotherapy, AML17 (2009-2014) and AML19 (2015-2020), involving 737 *NPM1*^{mut} patients (median age 52 years) of whom 286 had a *FLT3*-ITD. Both trials took place before the availability of approved *FLT3* inhibitors. In AML19 all patients underwent MRD testing after the first two courses of chemotherapy and, based on the findings from AML17,[14] only patients testing MRD^{+} in PB post-course 2 (PC2) were recommended for transplant in CR1 (unless they had adverse-risk cytogenetics). Patients who were MRD^{-} in PB continued with two courses of high-dose cytarabine consolidation. Patients from both trials could also be entered into a randomization to continue with *NPM1* MRD monitoring every 3 months for 2 years from the end of treatment. Overall, we observed significant heterogeneity of overall survival benefit from an allogeneic transplant in CR1 according to PC2 PB MRD status. While there was a substantial survival benefit for MRD^{+} patients undergoing alloSCT (3-year overall survival with CR1-alloSCT *vs*. without: 61% *vs*. 24%; hazard ratio [HR]=0.39; 95% confidence interval [95% CI]: 0.24-0.64; P<0.001) no benefit was seen for MRD^{-} patients (3-year overall survival with CR1-alloSCT *vs*. without: 79% *vs*. 82%; HR=0.82; 95% CI: 0.50-1.33; P=0.4) (Figure 2). Looking specifically at the 286 patients with *FLT3*-ITD co-mutations, 28% were PC2 PB MRD^{+} for *NPM1* and, again, those who received CR1-alloSCT benefited with a significantly better survival (3-year overall survival, 45% *vs*. 18%; HR=0.52; 95% CI: 0.29-0.93; P=0.03). In contrast there was no survival benefit for MRD^{-} patients: CR1-alloSCT was performed in 20% of the MRD^{-} patients and their 3-year overall survival was 83% compared to 76% for the patients who were not transplanted (HR=0.80; 95% CI: 0.37-1.71; P=0.6), CR1-allografting did reduce the cumulative incidence of relapse in MRD^{-} patients and improved relapse-free survival although no subgroup could be identified with a survival benefit from transplantation including those with a high *FLT3*-ITD allelic ratio (>0.5) or triple-mutated patients with a *DNMT3A* mutation or those with a high white cell count. However, as the majority of patients in these trials were <60 years of age these findings may not extend to older patients. Relapse occurred in 30%-40% of

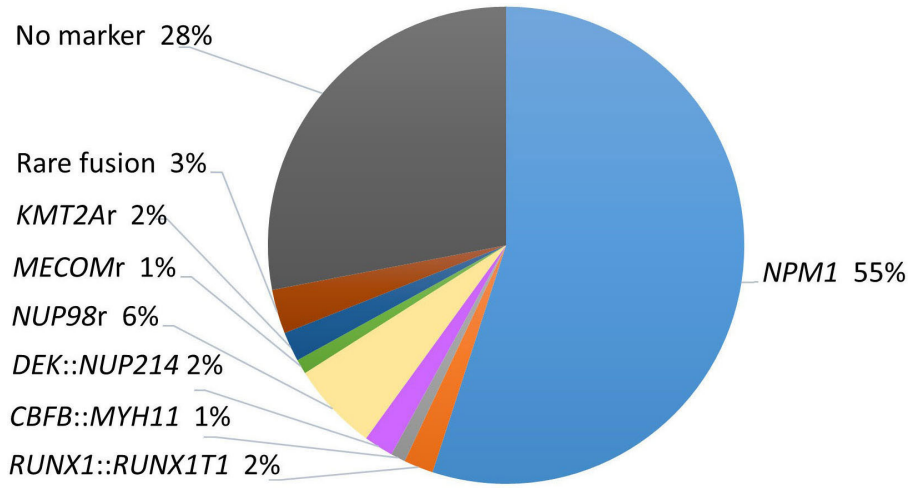

Figure 1. Co-occurring molecular lesions suitable for molecular minimal residual disease monitoring in *FLT3*-internal tandem duplication-mutated acute myeloid leukemia in the UK NRCI AML19 clinical trial cohort.

MRD^{-} patients not transplanted in CR1; of these, 60% went on to an allogeneic transplant in second complete remission with survival of 50% at 3 years, which was superior to that of relapsing MRD^{+} patients who had a poor outcome.

Recent data showing the prognostic impact of *FLT3*-ITD detection by ultra-sensitive next-generation sequencing may help provide additional prognostic information to that currently provided by *NPM1* MRD testing in assessing the risk of relapse in *NPM1*^{mut}/*FLT3*-ITD co-mutated cases.[17] Beyond the PC2 MRD assessment point, MRD^{-} patients not transplanted in CR1 should continue with MRD monitoring following subsequent cycles of consolidation.[18] Patients MRD^{-} in the PB at PC2 are frequently still positive in the bone marrow at that timepoint but become MRD^{-} with subsequent consolidation. Patients with persisting *NPM1* MRD positivity in the bone marrow at the end of treatment are at a higher risk of relapse and need close monitoring.[14,19] Using ELN definitions of molecular persistence at low copy number, Tiong *et al.*[20] reported that almost half of those with persisting positivity at the end of treatment become MRD^{-} on follow-up but those with a *FLT3*-ITD are at higher risk of disease progression and warrant consideration for pre-emptive treatment. An end-of-treatment bone marrow MRD assessment is therefore an additional checkpoint to further refine the decision to perform a CR1-alloSCT in *NPM1*^{mut}/*FLT3*-ITD^{+} patients.

For patients in remission a recent study has shown that prospective monitoring and treatment of MRD relapse improves survival in patients with *NPM1*^{mut}/*FLT3*-ITD^{+} AML. Potter *et al.*[12] randomized 637 patients from the UK NCRI AML17 and AML19 trials with a variety of molecular markers to undergo sequential molecular MRD monitoring during treatment and then for 3 years, or to continue with standard clinical care only with no molecular monitoring. Although there was no overall survival benefit for molecular monitoring in the whole population, a pre-specified subgroup analysis demonstrated a significant survival benefit for monitoring in the *NPM1*^{mut}/*FLT3*-ITD^{+} subgroup in which the

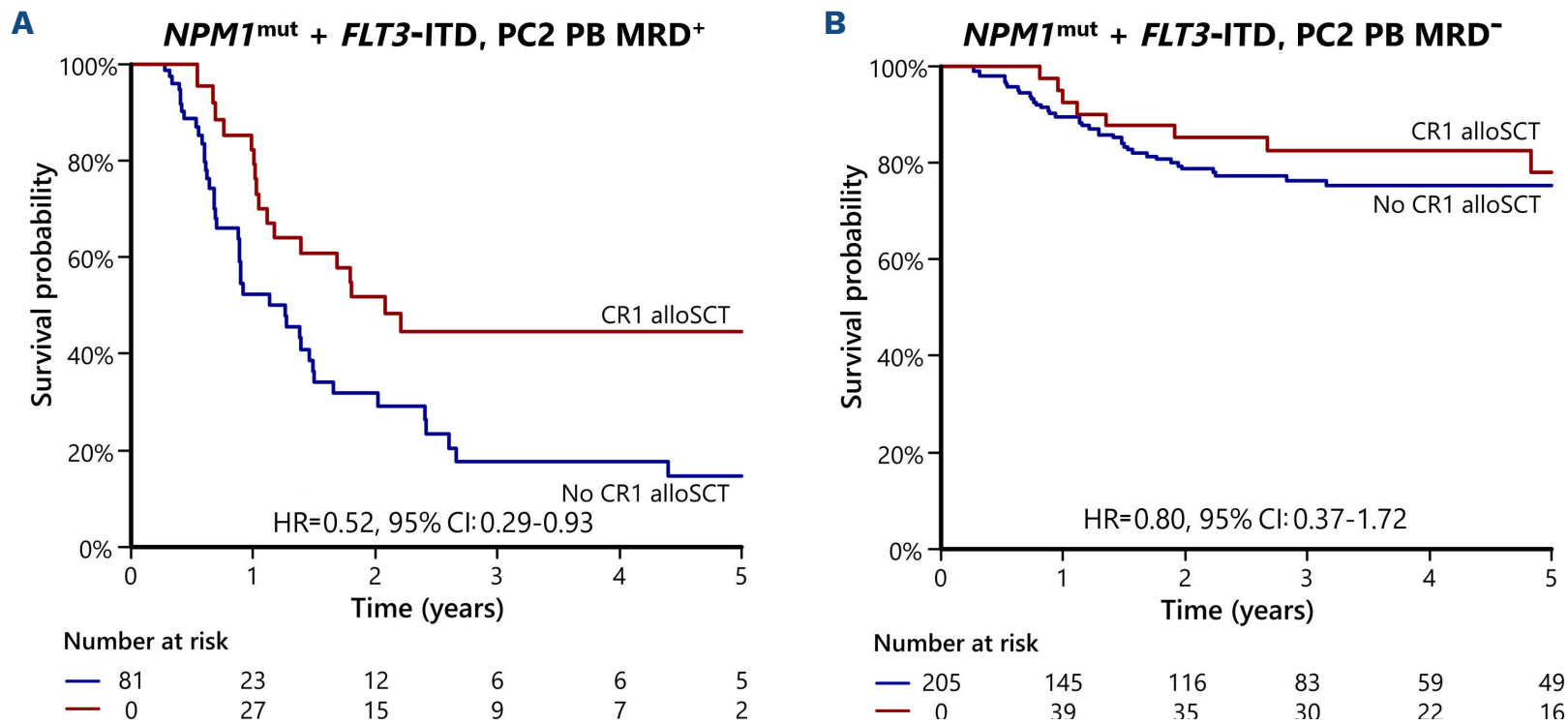

Figure 2. Overall survival based on receipt of allogeneic stem cell transplantation in first complete remission. Hazard ratios represent the hazard of death associated with allogeneic stem cell transplantation in first complete remission, from time-dependent Cox regression. (A, B) Simon-Makuch plots of overall survival of patients with *NPM1*-mutant and *FLT3*-ITD acute myeloid leukemia who were positive (A) or negative (B) for minimal residual disease in the peripheral blood after two courses of induction therapy divided according to whether they did or did not undergo allogeneic stem cell transplantation in first complete remission. Mut: mutated; ITD: internal tandem duplication; PC2: after course 2 of induction therapy; PB: peripheral blood; MRD: minimal residual disease; CR1 alloSCT: allogeneic stem cell transplantation in first complete remission; HR: hazard ratio; 95% CI: 95% confidence interval. Figure adapted from Othman *et al.*[16]

risk of death was almost halved.

For patients with *FLT3* mutations the therapeutic landscape has changed since these studies were performed with the approval of midostaurin and quizartinib for use with upfront chemotherapy and as single-agent maintenance.[21,22] The introduction of *FLT3* inhibitors into routine clinical practice has further called into question the therapeutic benefit of CR1-alloSCT, diminishing the relapse risk without transplant to <40% in selected *FLT3*-ITD-mutated subgroups. In the landmark phase III RATIFY trial, midostaurin was evaluated in combination with standard induction and consolidation chemotherapy and as maintenance in adults <60 years with *FLT3*-mutated AML.[21] There was a significant improvement in the primary endpoint of overall survival in all *FLT3* subgroups in the midostaurin arm. CR1-alloSCT for consolidation was not mandated, but all trial participants were eligible at the investigators' discretion, regardless of *FLT3* mutation status. Accordingly, in the midostaurin arm 28% of participants underwent a CR1-allograft, *versus* 22% in the placebo arm. In a retrospective analysis, the impact of CR1-alloSCT was evaluated and a strong beneficial effect for transplant was only found in the adverse-risk group.[23] Although these results should be interpreted with caution, as the trial was not powered for this particular subgroup analysis, this finding does support that transplantation can potentially be delayed until relapse in the favorable- and intermediate-risk groups. QuANTUM-First evaluated quizartinib with standard induction and consolidation chemotherapy and/or alloSCT, followed by maintenance therapy in *FLT3*-ITD-mutated AML.[22] Schlenk *et al.*[24] recently published a QuANTUM-First *post-hoc* analysis assessing the impact of CR1-alloSCT and quizartinib. Protocol-specified CR1-alloSCT was performed in 53% of patients. Multivariable analyses showed quizartinib and alloSCT as significant predictive factors for improved overall survival. Notably, patients with NPM1^{mut}/*FLT3*-ITD^{+} low allelic ratio were excluded from this group, because at the time the trial was conducted CR1-alloSCT was not recommended in this group.[25]

FLT3 inhibitors are able to induce deeper molecular responses when combined with upfront chemotherapy, thereby potentially reducing the proportion of MRD^{+} patients with a transplantation indication.[26] In the UK NCRI AML19v2 trial, in which midostaurin was combined with DAGO (daunorubcin, cytarabine plus gemtuzumab ozogamicin) induction, PC2 PB MRD negativity for *NPM1* was 80% compared to 68% in those receiving DAGO without midostaurin in the earlier AML19v1 trial.[27,28] Likewise, the availability of *FLT3* inhibitors as maintenance could also reduce the risk of relapse for MRD^{-} patients not transplanted in first remission.

A key objective of MRD monitoring is, however, to identify patients who are destined to relapse and instigate pre-emptive treatment while the patient is still well and in clinical remission.[29] For this purpose *NPM1* provides an ideal marker as the majority of molecular relapses allow a window of opportunity for intervention. In the UK NCRI AML17 and AML19 trials, which took place in an era (2012-2018) before

the widespread availability of *FLT3* inhibitors for the treatment of relapse, the most common intervention for MRD relapse was intensive salvage chemotherapy.[12] An alternative approach is to use targeted therapy with which outcomes may be better than those achieved at hematologic relapse. Othman *et al*.[30] reported on a series of 56 patients treated with *FLT3* inhibitors at molecular failure of *FLT3*-mutated AML: 60% had a molecular response and 45% achieving a complete molecular remission with the highest responses being seen in those with molecular relapse rather than molecular progression. Most patients were treated in the outpatient setting with low toxicity and approximately half were bridged to alloSCT with an overall survival of 80% at 2 years. In a separate study, patients undergoing molecular monitoring for *NPM1*^{mut} CBF-AML who received pre-emptive therapy at the time of molecular relapse had improved survival compared to those who received salvage therapy after having progressed from molecular to morphological relapse.[31] Importantly loss of *FLT3* mutations at relapse is reported to occur in almost 50% of patients receiving frontline *FLT3* inhibitors, so repeat testing at relapse is essential to optimize salvage therapy.[32]

CBF-AML are defined by the presence of either inv(16)(p13q22)/t(16;16)(p13;q22)/*CBFB*::*MYH11* or t(8;21)(q22;q22)/*RUNX1*::*RUNX1T1*. These leukemias are characterized by a high rate of complete remission and long-term cure and transplant is normally reserved for relapsed disease.[33,34] *FLT3*-ITD are present in approximately 2-3% patients with CBF-AML and do not alter the 2022 ELN favorable genetic risk assignment.[1,35] However, In a recent multicenter, retrospective study, Kayser *et al*.[36] suggested that patients with CBF-AML and *FLT3*-ITD co-mutation should not be classified as favorable risk, although notably very few had been treated with gemtuzumab ozogamicin or midostaurin and there was no evidence that alloSCT in CR1 improved overall survival. Both CBF fusion genes provide an ideal target for disease monitoring by reverse transcriptase quantitative polymerase chain reaction; however, importantly these transcripts may show persistent low-level expression after treatment and this is not predictive of relapse.[18] Therefore, unlike other molecular subtypes, the goal of treatment is to reduce levels below specific thresholds, rather than to achieve MRD negativity. Benefit for a CR1 transplant in CBF-AML has only been demonstrated for patients who have high-level MRD positivity after three or four cycles of treatment.[37] We recommend ongoing monitoring in the bone marrow every 2 months for the first year for patients with CBF-AML, particularly for those with a *FLT3*-ITD, then 3 monthly for another 2 years.[18]

To summarize, the questions of which patients with AML should receive an alloSCT and when this transplantation should take place are still being debated and represent a moving target as we incorporate new drugs and non-transplant outcomes improve. Although alloSCT remains the most effective antileukemic treatment available, other factors are relevant to any decision about the survival benefit of transplant in CR1 including the risk of relapse, the risk of the transplant itself and the prospects for successful salvage treatment if the patient does relapse. The 2022 ELN recommendations state that not only genetic abnormalities at the time of diagnosis but also results from MRD analyses should be taken into consideration for a comprehensive genetic risk assessment.[1] For some patients with *FLT3*-ITD, including those with *NPM1* mutations or CBF-AML, molecular MRD assessment at defined timepoints gives additional personalized information of the risk of relapse to inform choices of post-remission therapy, reserving transplant for relapse in MRD^{-} patients. This approach spares a significant number of patients the risk of transplant-related mortality and short- and long-term morbidity associated with alloSCT. Ongoing molecular MRD monitoring is an essential part of this strategy, allowing for early intervention if molecular relapse occurs. This strategy is being followed in the ongoing Optimise-*FLT3* trial in the UK, the results of which will provide further clarity to guide treatment decisions in *FLT3*-ITD-mutated AML in the current therapeutic and diagnostic era.

Disclosures

No conflicts of interest to disclose.

Contributions

NHR and KDL jointly wrote the manuscript

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