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ORAL ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

MRD Directed Treatment Intensification with Either FLAG-Ida or DA-Cladribine Improves Survival in Older AML Patients: Results from the NCRI AML18 Randomised Trial

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Background

Following intensive chemotherapy in acute myeloid leukemia (AML), residual disease, assessed by failure to achieve a remission (CR/CRi) or the presence of measurable residual disease (MRD) in remission identifies a poor risk group of patients. In the NCRI AML16 trial for older adults (>60yrs), patients who were MRD+ve by flow cytometry in their remission bone marrow after course 1 had significantly poorer survival (26% at 3yrs vs 42% if MRD-ve) due to a higher risk of relapse (Freeman *et al* JCO 2016). These results suggested that flow cytometric MRD after course 1, by identifying patients who have a poor outcome with standard therapy, could be used to risk stratify for further treatment. However, although not infrequently used, it is uncertain whether chemotherapy intensification is of benefit to older adults with residual disease.

In the AML18 trial we therefore conducted a course 2 randomization to evaluate MRD directed chemotherapy intensification in older adults.

Methods

AML18 patients who did not achieve MRD negativity after their first course (either not in CR/CRi or MRD+ve or MRD unknown) were randomized to either continue treatment with up to two courses of standard DA (Daunorubicin, AraC) (DA3+8 followed by DA2+5) or to receive up to 2 courses of intensified chemotherapy:- either FLAG-Ida or DA with Cladribine (DAC) (DA3+8, followed by DA2+5 both including Cladribine 5 mg/m ^{2} x 5 days). Course 1 had comprised DA (3+10) with 0, 1 or 2 doses of gemtuzumab ozogamicin. FLAG-Ida was dose reduced for patients over 70yrs and in course 3 for all patients (Fludarabine from 30mg/m ^{2} days 1-5 to 25mg/m ^{2} days 1-4, Idarubicin from 8mg/m ^{2} days 3-5 to 5mg/m ^{2} days 2-4). The DAC randomization was closed May 2019 due to drug supply issues.

The primary endpoint was overall survival (OS). Rate ratios (RR) were used when appropriate to account for non-proportional hazards effect. Secondary endpoints included conversion to MRD negativity (defined as undetectable MFC-MRD) following course 2.

Results

Between Nov 2014 and Jan 2023, 523 patients (median age 67yrs) entered this randomization (193 DA, 191 FLAG-Ida, 139 DAC) following course 1 response assessment. Of these patients 164 (31%) were not in CR/CRi, 260 (50%) were in CR/CRi MRD+ve and the remaining 99 (19%) were in CR/CRi but with MRD unknown (due to an absence of a leukaemia-associated-immunophenotype at diagnosis or inadequate/missing samples). 99/477 (21%) of patients had adverse risk cytogenetics. All characteristics were balanced between arms. Median follow-up was 51 months.

Following course 2, 47% (78/164) of those not in CR/CRi after course 1 converted to CR/CRi within 50 days: 55%, 57%, 34% for DA, DAC and FLAG-Ida respectively (DA vs DAC P=0.63, DA vs FLAG P=0.015). Of 282 patients providing MRD results after both course 1 and 2, 51% (60/117), 63% (50/79) and 58% (50/86) converted to MRD negativity after DA, DAC and FLAG-Ida respectively (DA vs DAC P=0.16, DA vs FLAG P=0.33). Greater hematological toxicity was seen with DAC or FLAG-Ida compared to DA (P<.001 for both platelet and neutrophil recovery). Day 60 mortality was increased in patients randomized to FLAG-Ida (9% vs 4% with DA and 4% with DAC, P=0.032). In total, 213 (41%) patients underwent allogeneic SCT (DA 42%, DAC 47%, Flag-Ida 35%).

OS at 5yrs was 27%, 32% and 32% for DA, DAC and Flag-Ida respectively (DAC vs DA HR=0.82 95%CI 0.62-1.09, P=0.174; FLAG-Ida vs DA HR=0.90 95%CI 0.70-1.16, P=0.407).

In subgroup analyses, comparing patients with known and unknown MRD status, there was no detectable survival benefit from intensification for MRD unknown patients (FLAG-Ida vs DA RR 1.52 95%CI 0.92-2.50, P value = 0.105; DAC vs DA RR 1.10, 95%CI 0.81-1.45, P value = 0.549).

In a sensitivity analysis, excluding patients with unknown MRD, there was a significant OS benefit for both DAC (OS at 5yrs, 32% vs 22% for DA; RR 0.84, 95%CI 0.77-0.98, P=0.029, Figure A) and FLAG-Ida (OS at 5yrs, 34% vs 23% for DA; RR 0.71, 95%CI 0.54-0.96, P=0.026, Figure B).

Conclusion

In older AML patients with evidence of residual disease following first induction, we saw a significant long-term survival benefit for intensified therapy with both DAC and FLAG-Ida in a randomized comparison with DA. This was despite early toxicity, observed particularly after FLAG-Ida. DAC intensification appeared better tolerated, delivered more patients to transplant and was associated with a greater conversion to MRD negativity.

Disclosures Russell: *Servier:* Honoraria; *Jazz Pharma:* Research Funding; *Pfizer:* Honoraria, Research Funding, Speakers Bureau; *Astellas:* Honoraria. **Andrew:** *AstraZeneca:* Current Employment. **Kelly:** *Otsuka:* Honoraria; *Biologix:* Honoraria, Speakers Bureau; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Astellas:* Honoraria, Speakers Bureau; *Pfizer:* Honoraria, Speakers Bureau; *Jazz:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sobi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Alexion:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau. **Mehta:** *Abbvie:* Honoraria, Speakers Bureau; *Pfizer:* Honoraria, Speakers Bureau; *Astellas:* Honoraria, Speakers Bureau; *JAZZ:* Honoraria, Speakers Bureau; *Servier:* Honoraria, Speakers Bureau; *Stemline:* Honoraria, Speakers Bureau. **Knapper:** *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Daiichi Sankyo:* Honoraria; *Jazz:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Tolero:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Freeman:** *BMS:* Research Funding; *JAZZ:* Research Funding, Speakers Bureau; *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.

OffLabel Disclosure: The label for cladribine does not include acute myeloid leukemia, however cladribine is frequently used to treat AML and related conditions. In this study cladribine is used in chemotherapy for the treatment of AML /high risk MDS.

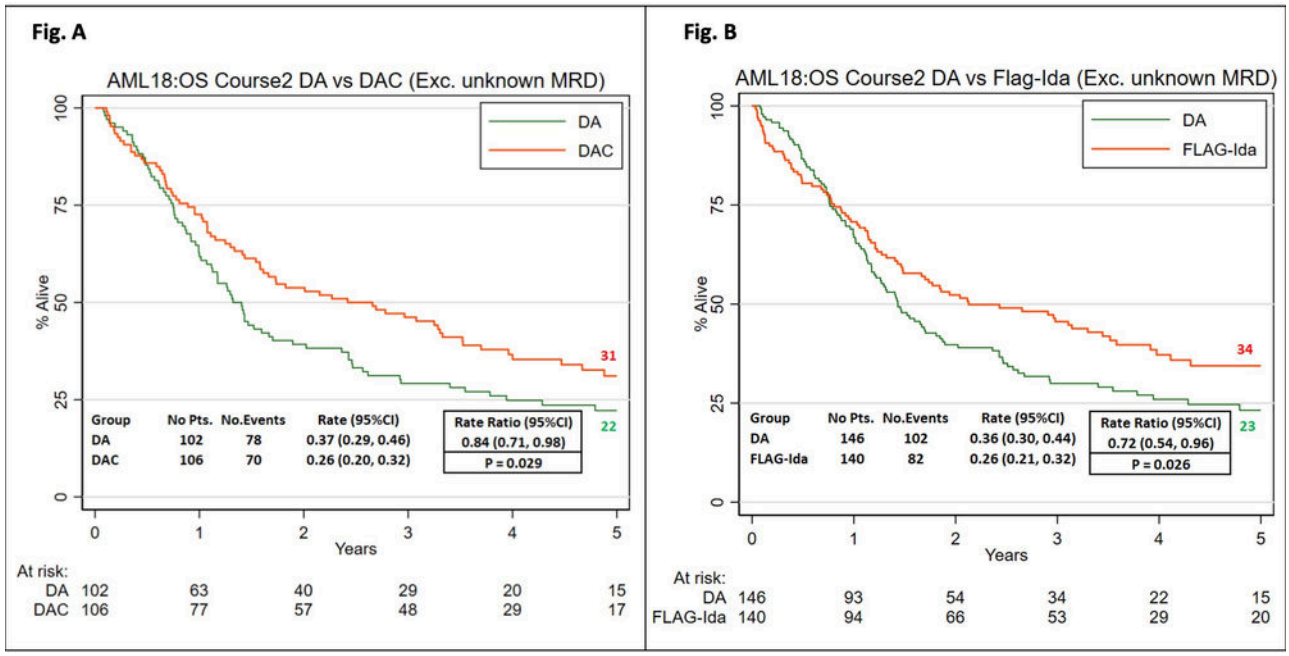

Figure 1

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