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P484 GEMTUZUMAB-BASED INDUCTION CHEMOTHERAPY COMBINED WITH MIDOSTAURIN FOR FLT3 MUTATED AML. UPDATED TOXICITY AND INTERIM SURVIVAL ANALYSIS FROM THE NCRI AML19V2 "MIDOTARG" PILOT TRIAL

Topic: 4. Acute myeloid leukemia - Clinical

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Background:

Following the RATIFY study, Midostaurin in combination with "7+3" like chemotherapy became the standard of care for patients with newly diagnosed *FLT3* mutated (mut) AML. The ALFA 0701 trial suggested a benefit for Gemtuzumab Ozogamicin (GO) in $FLT3^{mut}$ AML that was also apparent in a meta-analysis of GO in induction (Hills et al. JCO, 2014,15(9):986. The combination of GO-based induction with Midostaurin has not been formally assessed with respect to safety, response and survival in $FLT3^{mut}$ AML.

Aims:

To assess the safety and efficacy of Midostaurin and Gemtuzumab (in a single or fractionated dose) given with induction chemotherapy therapy in newly diagnosed $FLT3^{mut}$ AML.

Methods:

The NCRI AML19 v2 trial randomised patients generally aged 18-60y with newly diagnosed AML without known adverse karyotype to receive DA 3+10 (Daunorubicin 60mg/m^2 on days 1, 3 & 5 plus AraC 100mg/m^2 bd on days 1-10) plus either a single dose of GO (3mg/m^2 on day 1, DAGO1) or two doses (3mg/m^2, capped at 5mg on days 1 and 4, DAGO2). Patients with a *FLT3*-ITD or TKD could enter the "Midotarg" pilot and receive 50mg bd of Midostaurin (m) for 14 days following completion of chemotherapy, and following the second induction (DA 3+8 without GO) and 2 courses of HDAC consolidation and as maintenance for 12 cycles in non-transplanted patients. Patients with $FLT3^{ITD}$ without $NPM1^{mut}$ were recommended for allogeneic transplantation in CR1. Patients with $NPM1^{mut}$ were only recommended for transplant if MRD positive in the peripheral blood (PB) by RT-qPCR post course 2 (PB PC2+). From November 2020 to November 2021, 77 patients were enrolled into the Midotarg pilot receiving DAGO1m (n=39) or DAGO2m (n=38). 59 had a *FLT3* ITD and 22 a *FLT3*-TKD (and 4 had both). RT-qPCR MRD monitoring for patients with $NPM1^{mut}$ (n=48) was performed following each cycle of chemotherapy. Primary and key secondary endpoints were overall response rate (CR+CRi), MRD and overall survival (OS). Results were compared with an earlier cohort of 119 $FLT3^{mut}$ patients treated in AML19v1 with the same chemotherapy (DAGO1/DAGO2) without Midostaurin

Results:

Patients had a median age of 52 yrs. 16 (20%) were >60 yrs. We have previously reported that the combination

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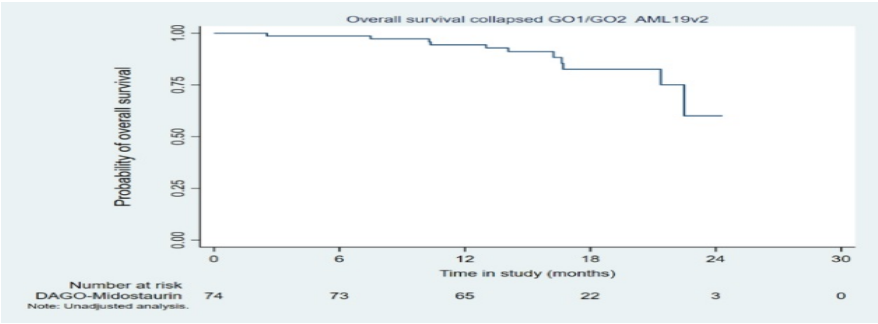
was well tolerated with no increase in haematological or non-haematological toxicity. Day 60 mortality was 0%. Overall response (CR + CRi) was achieved in 82% (DAGO1m) and 91% (DAGO2m). Median follow-up is 15 months. Estimated OS at 18 months was 82% (Figure 1) and was 81% and 84% for DAGO1m and DAGO2m respectively. This compares with 18m OS of 72% in patients treated with DAGO alone in AML19v1 (Figure 1) (68% DAGO1; 76% DAGO2).

46/77 evaluable patients had *NPM1*^{mut}, in these patients PB PC2 MRD negativity was 75% and 86% with DAGO1m and DAGO2m respectively . This compares with 61% and 74% in 65 evaluable patients with DAGO1 and DAGO2 without Midostaurin. End of treatment BM MRD negativity was 68% vs 74% for DAGO1m and DAGO2m respectively compared to 46% and 56% without Midostaurin.

Summary/Conclusion:

The addition of Midostaurin to DAGO1 and DAGO2 chemotherapy was safe in both younger and older patients with promising survival although follow up is short. The fractionated schedule (DAGO2) gave a higher proportion of MRD negativity post course 2 in patients with *FLT3*^{mut}/*NPM1*^{mut} and this is associated with a greatly reduced risk of relapse and death. DAGO2m is being taken forward in a randomised comparison against DA plus Midostaurin.

Figure 1a. Overall Survival in AML19v1 (DAGO1/DAGO2 combined) **Figure 1b.** Overall Survival in AML19v2 (Midotarg)



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