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Attenuated Arsenic Trioxide plus ATRA therapy for newly diagnosed and relapsed APL: long-term follow-up of the AML17 trial

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We have previously reported on the results of the NCRI AML17 Trial which for APL of all risk groups compared Anthracycline+ATRA (AIDA) vs the combination of Arsenic Trioxide (ATO) +ATRA, utilising an attenuated schedule of ATO¹. Here we present long term survival results for randomized patients and for 32 patients who received the same schedule of ATO + ATRA after relapsing from the AIDA arm. Ethics approval was provided by Wales REC 3, and all participants provided signed informed consent. From May 2009 to October 2013, 235 patients aged >16 years were randomized to either ATRA (45mg/m² in 2 divided doses)+ATO (8 week induction 0.3mg/kg d1-5 w1, 0.25mg/kg x2/w, w2-8, followed by 4 consolidation courses of 0.3mg/kg d1-5 w1, 0.25mg/kg x 2/w, w2-.4 (63 ATO doses) or the AIDA schedule: Idarubicin (Ida)12mg/m² d2,4,6,8 + ATRA to d60 (induction) then Ida 5mg/m² d1-4 + ATRA d1-15 (Course 2); Mitoxantrone 10mg/m² d1-5 + ATRA d1-15 (course 3); Ida 12mg/m² d1 + ATRA d1-15 (Course 4). ATRA was 45mg/m²/d in 2 divided doses. Maintenance was not given. High risk patients could receive a single dose of Gemtuzumab Ozogamicin (d1, 6mg/m²). An additional 70 patients were treated with AIDA after closure of the randomization. In total 189 patients were treated with AIDA of whom 33 relapsed and 32 were treated with the same schedule of ATO + ATRA receiving a median of 4 cycles (range 1-5). Follow-up is complete to 1 July 2017.

The median age was 47y (16-77); 57 had high risk APL (WBC>10x10⁹/L, 27 AIDA, 30 ATRA+ATO) and 49 (24 AIDA, 25 ATRA+ATO) were >60y. The results have not changed since our initial report¹ 91% entered morphological CR with no significant difference in CR rate between the arms (ATO+ATRA 94%, AIDA 89%; OR 0.54 (0.21-1.34), p= 0.18). With a longer median follow-up of 67.4 months the 5-year survival is now 92% (ATO+ATRA) v 86% (AIDA) (HR 0.71 (0.331.50) p=0.4; Figure 1A). Among patients who became MRD negative after consolidation, molecular relapse free survival is 97% vs 78% (HR 0.25 (0.12-0.52) p=0.0002; Figure 1B). No patient treated with ATRA+ATO who became

molecularly negative relapsed; among AIDA treated patients, 5-year cumulative incidence of any relapse (including molecular) was 20%. A significant reduction in frank relapse (1% vs 10% at 5 years, HR 0.18 (0.05-0.60) $p=0.005$) resulted in a better RFS for ATO (96% vs 86%, HR 0.43 (0.18-1.03) $p=0.06$; Figure 1C); the results are not affected by risk group (low risk 95% vs 87%, HR 0.58 (0.22-1.55) $p=0.3$; high risk 100% vs 83%, HR 0.12 (0.02-0.84) $p=0.03$; test for interaction $p=0.16$). With additional follow-up the molecular relapse risk with AIDA is higher than that observed in our previous AML15 trial (20% v 9%) where maintenance was employed² however the incidence of secondary AML/MDS was less in AML 17 (1% v 6%). No cases of secondary AML/MDS were seen after ATO+ATRA.

Of the 32 patients who relapsed following AIDA therapy, 1 died before treatment could be initiated and 31 (5 with concomitant CNS involvement) were treated with the same attenuated ATO schedule including 17 at molecular relapse. Their 5-year overall survival is 88% with a median follow-up of 44.9 months. All 31 patients achieved molecular CR of whom 5 patients received additional consolidation therapy with high dose cytarabine ($n=4$) or Gemtuzumab ozogamicin ($n=1$) after achieving molecular remission. 13 patients were transplanted in CR2 (10 autograft, 3 allograft) including 4 of the 5 patients with CNS disease and the 5 patients who had received additional chemotherapy. Of the 18 patients treated with ATO+ATRA alone without transplant or consolidation chemotherapy, 14 remain in molecular remission and 4 have relapsed (molecular in 3) Two patients have died, both transplanted; one 37 months post-allograft in second molecular remission, the other 36 months post-autograft in a patient who suffered a molecular relapse post-transplant. This patient had received only 1 course of ATO prior to autograft.

Genomic DNA was available from 31 patients who relapsed; paired diagnosis and haematological relapse samples were available from 8 patients and diagnostic material only from a further 23. We performed targeted next-

generation sequencing of a panel of 60 genes frequently mutated in AML. Molecular barcoded libraries were prepared using the HaloPlexHS system and sequenced using an Illumina HiSeq 2500 instrument. Alignment and variant calling was performed using Agilent SureCall v4 software. In parallel we performed PCR and fragment analysis to detect the FLT3 internal tandem duplication (ITD) as previously described.³. In keeping with previous reports, FLT3 ITD was the most frequent mutation and was detected in 14/31 patients (45%). Other recurrently mutated genes were WT1 in 7 patients (23%) NRAS in 3 (9.6%) and RUNX1 and KRAS in two patients each (6.4%). Profiling of the 5 patients who relapsed post salvage ATO showed no consistent findings, 2 had FLT3 ITDs, 1 had NRAS/KRAS mutations, 1 had a WT1 mutation and 1 had no mutations, suggesting that relapses post ATO are not predictable based on upfront genomic data.

The primary purpose of this updated analysis was to establish if an overall survival benefit for the ATO+ATRA has emerged as has been reported in the pivotal randomised APL0406 trial conducted in Italy and Germany by the GIMEMA, AML Study Group (AMLSG) and Study Alliance Leukaemia (SAL) cooperative groups^{4,5}. In AML17 although we found that the combination of ATO and ATRA continues to show a very low risk of relapse (1% at 5 years) irrespective of risk group with a significantly superior RFS compared to AIDA no overall survival benefit has emerged. These results are supported by a report from Abaza et al (2016) who also observed a very low relapse risk in both standard and high risk APL patients treated with ATO+ATRA supplemented by Gemtuzumab Ozogamicin (GO) in high risk patients⁶. In that study 46% of standard risk patients also received GO as treatment of leucocytosis, an intervention we used in only 6% of patients suggesting that GO makes a minimal contribution to the low relapse risk with ATO at least in standard risk disease.

In AML17 the lack of survival benefit resulted from the highly effective salvage intervention for AIDA-treated patients with ATO, with the majority of patients treated at molecular relapse, which could be explained by the emphasis on MRD monitoring. For patients treated with first line ATO and ATRA molecular monitoring is now of questionable value once molecular CR has been documented due to the low risk of relapse but molecular surveillance remains important in those who have had ATO salvage for relapse. The alternative ATO dosing used in AML17 resulted in fewer days on ATO treatment and a correspondingly lower cumulative dose and drug acquisition costs than the GIMEMA-AMLSG-SAL schedule despite the higher doses used in the first week of each course. This schedule proved highly effective as first line therapy not only in standard risk disease but also in high risk patients and at relapse. These results also question the role of transplantation as consolidation for relapsed patients as has been recommended⁷ at least in patients achieving molecular remission with ATO and ATRA who do not have CNS disease at relapse and who have received a full course of consolidation with ATO.

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Authorship:

AKB,NHR,RKH, DG designed the trial; JJ,RD,DG performed molecular monitoring; SB collated data; RKH analysed the data; NHR,MD entered patients; all authors contributed to the interpretation of the data and the writing and all apart from DG were able to undertake final review of the manuscript. There are no conflicts of interest to disclose.

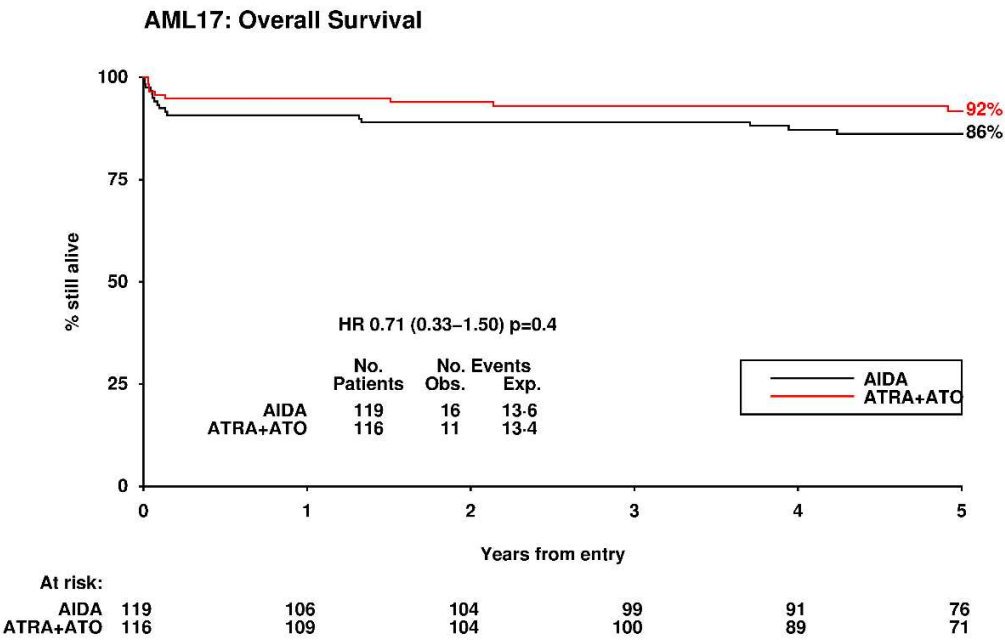
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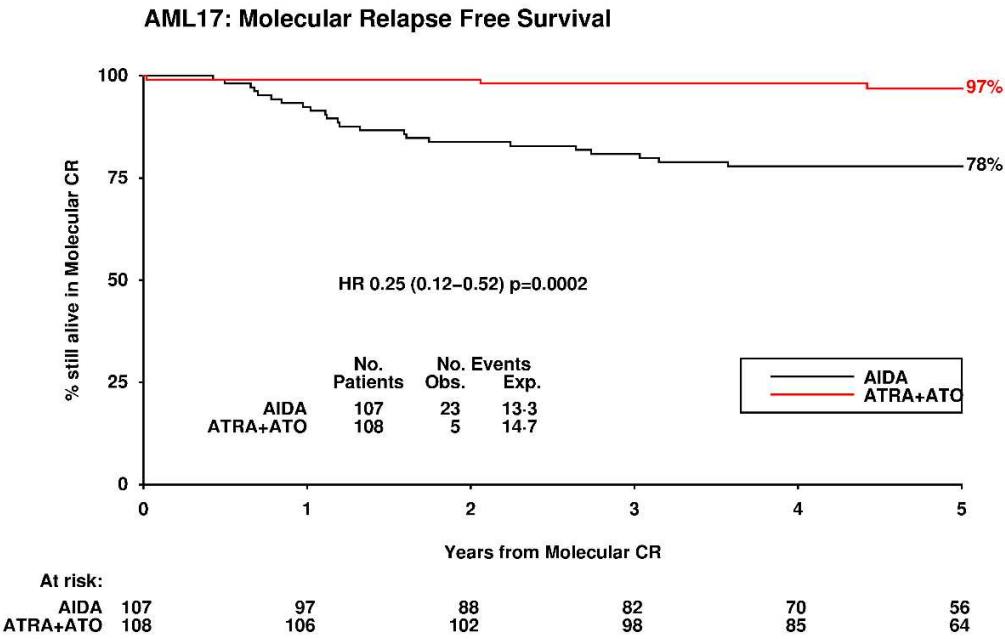
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Figure 1: Clinical Outcomes: A) Overall Survival for chemo-free vs AIDA approach; B) Molecular relapse free survival; C) Relapse Free Survival; D) Survival from relapse for relapsing AIDA patients treated with ATRA+ATO split by transplantation

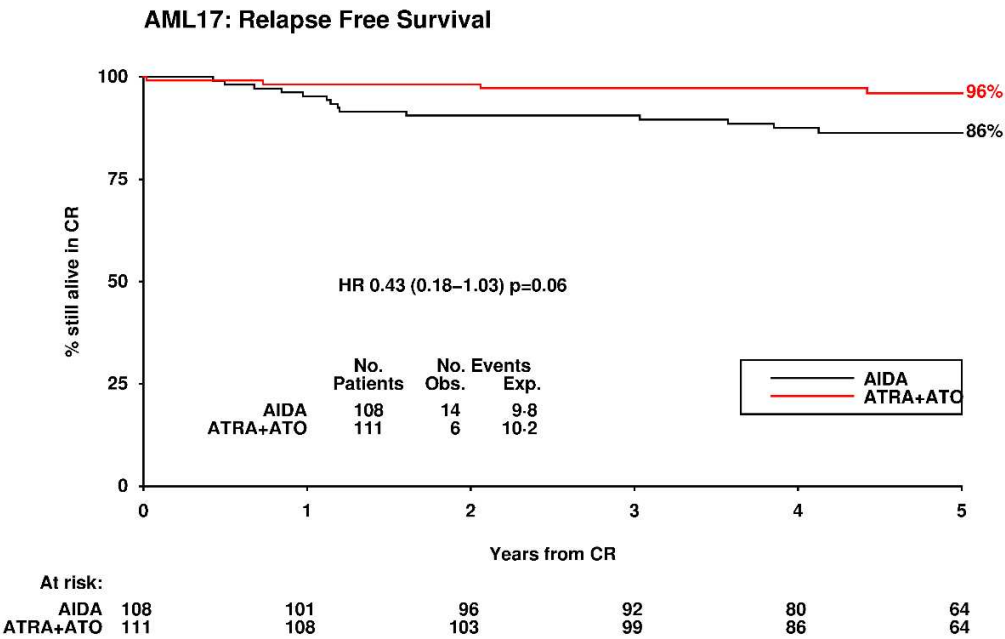
a)



b)



c)



d)

