Welcome to the latest AML trials newsletter
Once again, we would like to thank all those who have entered patients in the past and hope you will continue to contribute towards future improvements in outcome for patients with AML. None of the AML trials would be possible without the continued help and support of all of the AML collaborators, in the UK and abroad, to whom we would like to say a very big THANK YOU.

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AML-HR Results Published in Blood

Fludarabine and cytosine are less effective than standard ADE chemotherapy in high-risk acute myeloid leukaemia, and addition of G-CSF and ATRA are not beneficial: results of the MRC AML-HR randomized trial.

The optimum chemotherapy schedule for reinduction of patients with high-risk acute myeloid leukemia (relapsed, resistant/refractory, or adverse genetic disease) is uncertain. The MRC AML (Medical Research Council Acute Myeloid Leukaemia) Working Group designed a trial comparing fludarabine and high-dose cytosine (FLA) with standard chemotherapy comprising cytosine arabinoside, daunorubicin, and etoposide (ADE). Patients were also randomly assigned to receive filgrastim (G-CSF) from day 0 until neutrophil count was greater than 0.5 x 10^9/L (or for a maximum of 28 days) and all-trans retinoic acid (ATRA) for 90 days. Between 1998 and 2003, 405 patients were entered: 250 were randomly assigned between FLA and ADE; 356 to G-CSF versus no G-CSF; 362 to ATRA versus no ATRA. The complete remission rate was 61% with 4-year disease-free survival of 29%. There were no significant differences in the CR rate, deaths in CR, relapse rate, or DFS between ADE and FLA, although survival at 4 years was worse with FLA (16% versus 27%, P = .05). Neither the addition of ATRA nor G-CSF demonstrated any differences in the CR rate, relapse rate, DFS, or overall survival between the groups. In conclusion these findings indicate that FLA may be inferior to standard chemotherapy in high-risk AML and that the outcome is not improved with the addition of either G-CSF or ATRA.
AML16 received MREC approval on 16th December 2005 and a Clinical Trial Authorisation (CTA) from the MHRA on 19th September 2005. Cardiff University agreed to act as Sponsor for AML16 on 2nd December 2005.

The AML16 non-intensive randomisation LD Ara-C v LD Clofarabine will open to recruitment on Wednesday 16th August 2006. N.B. Patient surface area and hospital number are required for AML16 randomisations.

Already 132 centres from across the UK, as well as Denmark, New Zealand and South Africa, have started to get the approvals in place to join the AML16 trial. If any centres require information about joining the AML16 trial please do not hesitate to contact Noreen Akhtar, Tel: 0121 687 2309, Email N.Akhtar.2@bham.ac.uk, or see the AML16 website for further details www.aml16.bham.ac.uk.

AML16 Version 5 Released July 12th 2006

The first ‘Drug X’ to be added to the AML16 non-intensive randomisation is Arsenic Trioxide (ATO). Now Version 5 has been released centres can choose to enter patients into the five-way non-intensive randomisation:

Low Dose Ara-C v Low Dose Ara-C + Mylotarg v Low Dose Clofarabine v Low Dose Ara-C + Zarnestra v Low Dose Ara-C + ATO

or

Centres can choose to enter patients into any of the following pair-wise randomisations:

LD Ara-C v LD Ara-C + Mylotarg or
LD Ara-C v LD Clofarabine or
LD Ara-C v LD Ara-C + Zarnestra or
LD Ara-C v LD Ara-C + ATO

Therefore if a patient is, for example, not eligible for Mylotarg randomisation, one of the pair-wise randomisation options that does not include Mylotarg could be chosen.

Other changes:

- Redefinition of the reference laboratories for associated immunophenotypic and molecular studies.
- The intensive arm the study will open with Clofarabine daily dose of 20mg/m² rather than 30mg/m². Patients who enter the Clofarabine randomisation or are subsequently due to receive Clofarabine must have a normal serum creatinine on the day of treatment.
- Monitoring of methylation status will be performed using a peripheral blood sample. Azacytidine treatment will commence when the neutrophil count reaches 1.0 x 10⁹/l rather than 1.5 x 10⁹/l.

AML16 GCP and Site Files

All individuals involved in any aspect of the trial must be suitably qualified to be able to comply with GCP. Please make sure that all AML16 staff are able to comply with GCP by ensuring that they are appropriately GCP trained and that evidence of this training is kept in the AML16 Site File.

Please also ensure that the AML16 Site File contains a delegation log listing all the site personnel and their delegated roles. Up-to-date signed and dated CVs should be kept for all site personnel in the AML16 Site File.

When sites have all their AML16 documentation in place – SSA and R&D approval, countersigned site agreements and Centre Registration Forms they will be sent an Induction Pack by the Chief Investigator, Professor Alan Burnett, which will include further information regarding Site File requirements.
AML15 is open to patients up to the age of 59 (or older if considered suitable for intensive therapy) with any form of de novo or secondary AML. AML15 opened to recruitment in May 2002. By the 1st August 2006, 2070 patients had been randomised from 168 centres. 74 paediatric patients have been entered. AML15 continues recruit extremely well. On average over the past year 54 patients have been recruited per month.

AML15 Protocol Version 5 Released 1st July 2006
As sufficient patients had been recruited to the induction Mylotarg randomisation, this closed on 30th June 2006. N.B. The Mylotarg randomisation in consolidation remains open. The amendment introduces a randomised comparison for patients who have a FLT-3 mutation. Patients will be randomised to receive or not the FLT-3 inhibitor CEP-701 (Lestaurtinib) which will be given orally bd after each course of chemotherapy for up to 28 days. We will inform all AML15 Collaborators when this randomisation is scheduled to open. The amendment clarifies that high risk patients are eligible for an allograft from an unrelated as well as a sibling donor, and clarifies that Methotrexate can be given orally in the APL maintenance arm.

Dr Leach and his team from Western Infirmary, Glasgow who randomised the 2000th patient on 26th June 2006
AML14

AML14 is a randomised trial for patients with AML or high risk MDS, primarily, but not exclusively, over 60 years of age. AML14 opened to recruitment in December 1998. The intensive arm of the AML14 trial closed 20/05/05 with 1273 patients randomised. The original non-intensive arm closed on 01/12/03 with 213 patients randomised.

108 patients have been randomised into AML14 non-intensive comparing LD Ara-C +/- Mylotarg but Mylotarg supplies are currently unavailable so the randomisation has been suspended. (N.B. Mylotarg supplies for AML15 are unaffected). The LD Ara-C +/- Mylotarg comparison is a phase 2 randomised study which is not powered to give a definitive answer, but will provide useful information and will be continued in the AML16 trial. It is unlikely that the AML14 non-intensive trial will reopen but the comparison will be part of AML16 non-intensive when the trial starts and Mylotarg supplies are available.

The following paediatric paper using AML trial data has recently been published.

Treatment for myeloid leukaemia of Down syndrome: population-based experience in the UK and results from the Medical Research Council AML 10 and AML 12 trials.

Down syndrome (DS) children are at an increased risk of developing myelodyplasia and acute myeloid leukaemia (AML). We retrospectively analysed the population-based data on 81 children with myeloid leukaemia of Down syndrome (ML-DS) from the UK National Registry of Childhood Tumours and experience in the Medical Research Council (MRC) AML 10 and AML 12 trials, which enrolled 46 children with ML-DS from 1988 to 2002. Eight per cent of UK children with AML had DS, but DS children comprised only 5% of children registered in MRC trials. The unique clinical characteristics of ML-DS were confirmed. Overall survival (OS) of ML-DS at 5 years increased from 47% in UK children diagnosed from 1988 to 1995 to 75% in children diagnosed from 1996 to 2002. OS for DS children registered in AML 10 and AML 12 was 74% in 5 years and improved from AML 10 to AML 12 (56% vs. 83%) There was no significant difference in OS between DS and non-DS children (OS: 74% vs. 62%, P = 0.4) in the trials, but this result masked a significant increase in early death amongst DS children, with a significant reduction in mortality later on. Relapse was significantly reduced (3% vs. 39%, P = 0.0003), leading to the improved disease-free survival (83% vs. 56%, P = 0.02). Given the increased number of early treatment-related deaths, future treatment protocols should aim to reduce chemotherapy dosage or intensity whilst maintaining low rates of resistant and recurrent disease.

If you know of anyone involved in AML Trials that hasn’t received a copy of this newsletter and would like a copy please contact the AML Trials Team.

The AML Trials Team are always here to help. Please find our contact details below.

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