The Acute Myeloid Leukaemia trials

Background

Acute Myeloid Leukaemia and High Risk Myelodysplasia are primarily diseases of the elderly. Although there have been gradual improvements in rates of initial over time, very few patients survive beyond 5 years. Considerable numbers of patients with these diseases have not been entered into previous clinical trials since there is uncertainty as to whether intensive chemotherapy will be either tolerated or beneficial.

The evidence consistently showed that patients with high risk AML do poorly with conventional therapy. It is therefore appropriate to test alternative therapies in such patients.

AML-HR recruited all patients with resistant, refractory, relapsed or adverse cytogenetic AML. The different chemotherapy regimes are detailed below.

The AML15 trial recruited patients aged less than 60 years, whether adults or children, and also to patients aged 60 years or over for whom intensive therapy was considered appropriate. The different chemotherapy regimes are detailed below.

The AML14 and AML16 Trials evaluated two treatment strategies, an Intensive and a Non-Intensive approach. Where there is uncertainty, patients with AML or High Risk MDS (>10% blasts) primarily, but not exclusively, over 60 years of age, will be randomised between the Intensive and the Non-Intensive treatment approaches. The different chemotherapy regimes are detailed below.

Trials in AML are long term undertakings. The AML trials were managed by Birmingham Clinical Trials Unit between 2000 and 2009. The long term follow-up and all future AML trials are now undertaken by the Haematology Clinical Trials Unit at Cardiff University. **http://medicine.cf.ac.uk/cancer-genetics/heamatology/research/clinical-trials-aml/ (http://medicine.cf.ac.uk/cancer-genetics/heamatology/research/clinical-trials-aml/)**

Please see the AML16 Contacts page (/research/activity/mds/trials/bctu/trials/portfolio-v/aml16/contact/index.aspx) for further information.

Online data entry is available for AML15 here (https://www.trials.bham.ac.uk/AML15) .

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What were the AML trials at BCTU...

AML-HR

At entry patients were randomised to any, or all, of three treatment comparisons: ADE versus FLA; G CSF versus not and ATRA versus not. Patients received 2 courses of their allocated therapy. Patients who were then in complete remission after 2 courses received consolidation with either high dose Ara C or transplantation.
The AMLHR closed in 2003 with 406 patients randomised.

AML14

The Intensive treatment arm compared two doses of Daunorubicin (50 mg/m2 vs 35 mg/m2), two doses of Cytosine Arabinoside (200 mg/m2 vs 400 mg/m2), and three versus four courses of treatment in total. The Non-Intensive treatment arm compared scheduled Low Dose Cytosine Arabinoside versus scheduled Low Dose Cytosine Arabinoside plus the immunoconjugate Gemtuzumab Ozogamicin (GO).
The non-intensive randomisation closed to recruitment in 2006 with 321 patients in total, and the intensive arm closed in 2005 with 1273 participants.

AML15

Through the use of an efficient factorial design, AML15 evaluated several relevant therapeutic questions in AML. For patients who did not have the Acute Promyelocytic (APL) subtype, an induction randomisation compared the standard ADE and DA regimens. Patients who had a FLT3 mutation at diagnosis were randomised to combine, or not, a FLT3 inhibitor after each course of the allocated induction and consolidation chemotherapy. A consolidation randomisation compared MRC chemotherapy (MACE + MidAC) with high-dose Ara-C. The 4 versus 5 courses randomisation from AML12 continued in patients under 45 years, but the fifth course was Ara-C. The role of the immunoconjugate Mylotarg was evaluated in consolidation (course 3) in patients who did not enter the FLT3 inhibitor randomisation. The role of allogeneic transplant, either standard or “mini”, was assessed in standard and poor risk patients.
The AML15 trial closed in 2009 with 3484 patients randomised from 162 centres.

AML16

The intensive approach compared two standard chemotherapy schedules DA (Daunorubicin/Ara-C) with ADE (Daunorubicin/Ara- C/Etoposide). In addition, the role of all-trans-retinoic Acid (ATRA) in combination with these treatments in the first induction course was evaluated. Patients who achieved complete remission (CR) or partial remission (PR) after course one received a second course of the same treatment with the ATRA if allocated to do so, and were then randomised to one further course or not and were be eligible for a non-intensive allogeneic stem cell transplant if a suitable HLA matched donor was available. Patients who failed to achieve a CR or PR after course 1 and were in CR after course 2 received course 3. Patients who didn’t have a donor were randomised to maintenance with Azacytidine or not.

Patients who were not considered fit for an intensive treatment approach were randomised between an established approach to non-intensive treatment, namely Low Dose Ara-C versus one of two novel treatments, which are Low Dose Clofarabine or Sapacitabine.
The non-intensive randomisation closed to recruitment in 2011 with 902 patients in total, and the intensive arm closed in 2012 with 1881 participants.

What did the studies find...

AMLHR

Neither the addition of ATRA nor G-CSF demonstrated any differences in the complete remission rate, relapse rate, disease free survival period, or overall survival between the groups. The authors concluded 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.

AML14

AML14 found that neither dose escalation during induction nor extended treatment during consolidation improved patient outcome and concluded that progress in improving survival rates in the older patient requires the development of new treatment strategies. Treatments are needed that exert a more selective anti-leukaemic activity whilst not suppressing normal blood cell development or having significant adverse reactions.

AML15

Although longer follow up is required there is ample evidence from AML15 that the FLAG-Ida schedule was significantly decreased normal blood cell production and required more supportive care with the associated economic implications. Preliminary analysis does not suggest that any potential benefit would out weigh this. It is possible that later benefits may emerge. The addition of Mylotarg to induction course 1, initially at least, significantly reduced the risk of relapse and improved the disease free survival period, which translated into a significant overall survival advantage for 70% of the patients. AML15 compared four versus five courses and did not find a significant benefit of adding a fifth treatment course.

What impact did these studies have...

There has been important progress in the treatment of Acute Myeloid Leukaemia (AML) in patients under 60 years. A remission rate of 80% can be achieved by several schedules, and 40-45% of patients diagnosed will survive. Improvements in older patients have been less detectable.

All AML trials build upon the success and results of the previous. It is clear that AML15 was a highly successful trial with recruitment at an unprecedented level (60 patients per month), a high overall complete remission rate of 84%, and survival which is significantly improved compared with the previous MRC AML12 trial. Thus, the therapy used in AML15 forms the backbone of the AML17 trial, now managed at Cardiff University.

http://aml17.cardiff.ac.uk/ (http://aml17.cardiff.ac.uk/)

Publications...

Milligan DW, Wheatley K, Littlewood T, Craig JIO, Burnett AK. Fludarabine and cytosine are less effective than standard ADE chemotherapy in high-risk acute myeloid leukemia, and addition of G-CSF and ATRA are not beneficial: results of the MRC AML-HR randomized trial. Blood 2006; 107: 4614-4622.
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http://www.ncbi.nlm.nih.gov/pubmed/21172891 (http://www.ncbi.nlm.nih.gov/pubmed/21172891)

Funders and Working Groups...

Medical Research Council - **www.mrc.ac.uk (http://www.mrc.ac.uk)**

Leukaemia and Lymphoma Research (formerly Leukaemia Research Fund)
http://leukaemialymphomaresearch.org.uk/ (http://leukaemialymphomaresearch.org.uk/)

For more information...

Leukaemia and Lymphoma Research - **http://leukaemialymphomaresearch.org.uk/ (http://leukaemialymphomaresearch.org.uk/)**
MacMillan Cancer Support - **http://www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx (http://www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx)**

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