FINAL STUDY REPORT

Study Title: Phase I dose escalation study of clofarabine and liposomal daunorubicin in childhood and adolescent Acute Myeloid Leukaemia

Chief Investigator:	Dr Pamela Kearns
Sponsor:	University of Birmingham
Sponsor's Protocol No:	RG_08-016
REC reference No:	08/H1208/36
CTA No:	21761/0221/001-001
EudraCT No:	2008-002288-14

First Study Approval by MREC:	28th November 2008
First Study Approval by MHRA:	7th January 2009
Substantial Amendments to Date:	Amendment 01: 23rd December 2008 Amendment 02: 10th February 2009 Amendment 03: 18th March 2010

Number of patients expected:	18
Number of patients recruited:	13

Opened sites:
Alder Hey Children's Hospital, Liverpool – opened 02/06/2009
Birmingham Children's hospital, Birmingham – opened 23/02/2009
Bristol Royal Hospital for Sick Children – opened 17/06/2009
Royal Marsden Hospital, London – opened 04/03/2009
Great Ormond Street Hospital, London – opened 25/03/2009
St James' Hospital, Leeds – opened 04/03/2009
Royal Victoria Infirmary, Newcastle – opened 15/07/2009
Royal Manchester children's Hospital – opened 18/08/2009
Royal Hospital for Sick Children, Glasgow – opened 30/11/2009

Study End date: 30th June 2011

Publications

Publication of final analysis of trial planned for Q1 2012

Abstracts

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Phase I Study of Clofarabine and Liposomal Daunorubicin in Childhood Acute Myeloid Leukemia (AML)
Poster presentation American Society Clinical Oncology (ASCO) conference 2nd – 7th May 2010

P. Kearns, N. J. Graham, M. Cummins, B. Gibson, J. Grainger, R. Keenan, D. Lancaster, G. Shenton, J. Vormoor, D. Webb, I. Hawley, P. J. Johnson;
Phase I study of clofarabine and liposomal daunorubicin in childhood acute myeloid leukaemia.
Poster discussion presentation, American Society Clinical Oncology (ASCO) conference 3rd – 7th June 2011

Objective

This was a phase I, single arm, multicentre study of clofarabine and liposomal daunorubicin in patients with acute myeloid leukaemia (AML) in relapse or refractory to induction therapy. The main objectives of the trial were to assess the safety and tolerability of clofarabine when used in combination with liposomal daunorubicin, describe the overall response rate and durability of response to include the number of patients that undergo stem cell transplant after re-induction with clofarabine and liposomal daunorubicin.

Methodology

This was a phase I study using the 3+3 design to determine the safety and toxicity of the study drugs in patients with relapsed or refractory acute myeloid leukaemia

All parents/guardians and /or patients gave written informed consent for entry into the study before any study specific procedures were performed.

Each patient received a 2 hour infusion of clofarabine on days 1-5
Patients also received liposomal daunorubicin as a fixed dose of 60mg/m2/day at each level on days 1, 3 and 5 this was given intravenously over 2 hours and was started 4 hours after the start of the clofarabine infusion.

The following clofarabine dose levels were studied;
Dose level 0: 30mg/m^2 /day for 5 days
Dose level 1: 40mg/m^2/day for 5 days

There was also a de-escalation dose level (level -1) of 20mg/m^2/day which could have been used if patients had experienced unacceptable toxicity at dose level 0.

All patients received a single cycle of treatment.

Each cohort required a minimum of 3 patients and if 2 patients in a cohort of no more than 6 developed dose limiting toxicities no further dose escalations were allowed and the prior dose level would be expanded to 6 patients.

Assessments of toxicity, using common toxicity criteria version 3.0, were ongoing during the patient hospitalisation. The patients were then followed up until further treatment was received or disease progression.

Haematological toxicity was assessed in responding patients. Haematological toxicity is defined as the development of grade 4 neutropenia (<$0.5x10^9$/l) or grade 4 thrombocytopenia (<$25x10^9$/l) due to a hypoplastic marrow at 6 weeks, in the absence of leukaemia. A bone marrow examination was performed after day 21, when there were signs of bone marrow recovery. If the myelosuppression persisted

beyond day 35 a bone marrow aspirate was performed by day 42 to exclude leukemic infiltration

Main parameters of safety

Assessments of toxicity were ongoing during the patient hospitalisation. The patients were then followed up until further treatment was received or disease progression.

Adverse Events and Laboratory Parameters

Main parameters of efficacy

The efficacy of the treatment was defined by the following criteria

Complete remission (CR) all of the following must have been achieved

- ANC $\geq$ 1.0 x 10^9/L
- Platelet count $\geq$ 100 x 10^9/L
- Bone Marrow < 5% blasts

Complete remission with incomplete blood count recovery (CRi)

- Neutrophil and platelet recovery is not achieved but all criteria for CT is (i.e. < 5%blasts)

Partial remission (PR)

- Peripheral blood count recovery as for CR, but with decrease in marrow blasts of >50% and not more than 5-25% abnormal cells in the bone marrow aspirate.

Recruitment

It was planned to recruit up to maximum of 18 patients to this study, the number of recruited patients depending on the dose escalations and dose limiting toxicities. A total of 13 patients were recruited all of whom received the required 1 cycle of clofarabine and lipsomal daunorubicin. Six patients were recruited to the first dose level 0 and 7 patients recruited to dose level 1. The trial closed as the the safety and efficacy of this agent was established at dose level 1.

Tolerability and Toxicity

There were 24 serious adverse events in total. The majority of events were expected and were secondary to myelosupression related to the study drugs. The most common SAE was neutropenic fever.

One SUSAR was reported for late cardiac toxicity. This occurred in a patient who had a complete remission and went on the have an allogeneic bone marrow transplant. The patient developed cardiac failure 12 months post BMT. Although there had been additional treatment, the contribution of the study drugs to the SAE could not be excluded.

SAE reference number	Description of SAE	Category
HM1006/001/01	Febrile Neutropenia	IMP - SAR
HM1006/002/01	Febrile neutropenia	IMP - SAR
HM1006/003/01	Neutropenia (gd 4)	IMP - SAR

HM1006/003/02	Infection	IMP - SAR
HM1006/003/03	Thrombocytopenia	IMP - SAR
HM1006/003/04	Cardiac failure	IMP - SUSAR
HM1006/005/02	Increased papular and skin rash	Unrelated SAE
HM1006/006/01	Febrile neutropenia	IMP - SAR
HM1006/006/02	Thrombocytopenia / anaemia	IMP - SAR
HM1006/007/01	Infection	IMP - SAR
HM1006/007/02	Febrile neutropenia	Unrelated SAE
HM1006/007/03	PR bleed	IMP - SAR
HM1006/008/01	Febrile neutropenia	IMP - SAR
HM1006/009/01	Febrile neutropenia	IMP - SAR
HM1006/009/02	Febrile neutropenia	IMP - SAR
HM1006/009/03	Febrile neutropenia	IMP - SAR
HM1006/009/04	VII cranial nerve lower motor neurone palsy	Unrelated SAE
HM1006/0010/01	Febrile with associated rigours	IMP - SAR
HM1006/0010/02	Acute respiratory arrest	Unrelated SAE
HM1006/0010/03	Disease related death	Unrelated SAE
HM1006/0011/01	Febrile neutropenia	IMP - SAR
HM1006/0011/02	Febrile neutropenia	IMP - SAR
HM1006/0012/01	Febrile neutropenia	IMP - SAR
HM21006/0013/01	Febrile neutropenia	IMP - SAR

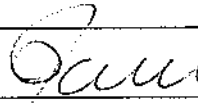
Clinical Responses

From the 13 patients recruited into the study, 5 showed a response to the combination of clofarabine and liposomal daunorubicin, including 2 patients with CR, 2 patients with CRi and 1 PR. One patient was not evaluable because the Investigator gave alternative chemotherapy during the evaluation period because inadequate response was suspected on the basis of the cytogenetic analyses.

Conclusion

The clofarabine and liposomal daunorubicin combination appeared to be well tolerated even in heavily pre-treated patients, with no dose limiting toxicities observed at the 30mg/m^2 or the 40mg/m^2 dose levels.
Complete responses were observed, which allowed these patients to proceed to bone marrow transplant. The data from this trial will allow the future evaluation of the regimen in under 16 year olds in front line and second line AML clinical trials.

Declaration

Signature of Chief Investigator:	
Print name:	P. Kearns.
Date:	8/2/12