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SHORT REPORT

A randomised comparison of FLAG-Ida versus daunorubicin combined with clofarabine in relapsed or refractory acute myeloid leukaemia: Results from the UK NCRI AML17 trial

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Summary

The prognosis for younger patients with relapsed acute myeloid leukaemia (AML) is generally dismal. Allogeneic stem cell transplantation is the preferred therapy for these patients. As part of the UK NCRI AML17 trial, daunorubicin/clofarabine (DClo) was compared with fludarabine, cytarabine, granulocyte colony-stimulating factor with idarubicin (FLAG-Ida) in 311 patients designated high-risk following course one of induction therapy, which has previously been reported. We now report the results of the same randomisation in patients who were refractory to two induction courses or subsequently relapsed. A total of 94 relapsed or refractory AML patients, usually less than 60 years of age and with mainly favourable or intermediate-risk cytogenetics, were randomised to receive up to three courses of DClo or FLAG-Ida, with the aim of proceeding to transplant. Complete remission was achieved in 74% of patients with no difference between the arms. Overall, 57% of patients received a transplant with no difference between the arms, likewise overall survival at five years showed no significant difference (21% for DClo vs. 22% for FLAG-Ida). No patient who did not receive a transplant survived beyond 21 months. A stratified analysis including the 311 post course 1 high-risk patients who underwent the same randomisation showed a consistent treatment benefit for FLAG-Ida.

KEYWORDS
chronic lymphocytic leukaemia, morphology, CLL lymphocytes

INTRODUCTION

Patients with relapsed and refractory acute myeloid leukaemia (AML) represent an important unmet therapeutic need, for which there is no universally accepted standard of care. European Leukemia Network (ELN) guidelines suggest a number of regimens including intermediate-dose cytarabine with our without an anthracycline, MEC [mitoxantrone, etoposide and cytosine arabinoside (Ara-C)] or fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) with idarubicin (FLAG-Ida).[1] Furthermore, several new chemotherapy drugs having failed to improve survival in randomised studies against standard regimens[2,3] although the *FLT3* inhibitor giltertitinib was found to be superior to chemotherapy in relapsed *FLT3*-mutated AML.[4] Recently FLAG-Ida combined with venetoclax has been reported as having promising results in both newly diagnosed and relapsed/refractory AML.[5]

The challenge with relapsed/refractory AML is twofold. Firstly to improve the remission rate and secondly to deliver more patients to transplant which is the only curative option for the majority of patients. For relapsed patients the FLAG-Ida (fludarabine/ara-C/GCSF and idarubicin) has been widely used[1] and in our MRC AML15 trial FLAG-Ida given for the first two treatment courses had a significantly superior anti-leukaemia effect when compared to '7 + 3'-like chemotherapy[6] In the AML17 trial we chose as the comparative treatment to replace Ara-C in a daunorubicin/Ara-C combination, with the alternative nucleoside, clofarabine.

Clofarabine (2-chloro-2′-fluoro-deoxy-9-β-D-arabinofuranosyladenine) is a novel nucleoside analogue developed as the result of a series of chemical modifications to minimise cleavage while retaining activity.[7] Although not approved as upfront therapy in AML despite activity in adverse-risk disease[8,9] promising results have been reported when given in combination with Ara-C and GCSF (GCLAC regimen) in the relapsed setting.[10] Following a feasibility study combining daunorubicin with clofarabine (DClo), we prospectively compared the combination with FLAG-Ida in both high-risk AML following course 1 of induction and in relapsed/refractory patients who had previously entered the AML17 trial. The high-risk experience has previously been reported.[11] Here we report on the outcome of the relapsed and refractory patients.

PATIENTS AND METHODS

As part of the UK National Cancer Research Institute (NCRI) AML17 trial (ISRCTN55675535) designed primarily for patients under 60years of age with untreated *de novo* or secondary AML and high-risk myelodysplastic syndrome (defined as >10% marrow blasts at diagnosis), patients who were high-risk post course1 ($n = 311$) could enter a randomisation to compare FLAG-Ida with DClo. In addition, this randomisation was open to patients in first morphological relapse and to those who were refractory to two courses of induction chemotherapy. Patients who entered the high-risk randomisation in CR1 were not eligible to re-enter the randomisation if they subsequently relapsed. Patients older than 60 years could enter the trial if considered fit for intensive therapy.

The trial was conducted in accordance with the Declaration of Helsinki, was sponsored by Cardiff University, and was approved by the Wales Research Ethic Committee 3. All patients provided written informed consent to random assignment. Patients needed to be aged over 16 years at trial entry. Relapse of disease was defined as more than 5% blasts in the marrow. Patients who relapsed after treatment in NCRI trials prior to AML17 could be included. Patients were randomly assigned in a 2:1 ratio to DClo or FLAG-Ida, each for up to three courses stratified by baseline information. The intention was that every patient would be eligible to proceed to allogeneic transplant. Consenting patients were randomised[1,2] to receive up to three courses of DClo (daunorubicin 50 mg/m^2 on days 1, 3 and 5 and clofarabine 20 mg/m^2 ^{on} days 1–5) or FLAG-Ida (fludarabine 30mg/m^2 on days 2–6, Ara-C 2g/m^2 on days 2–6, GCSF 263 μg on days 1–7, idarubicin 8 mg/m^2 on days 4–6).

Statistical methods

The primary outcome measures for the trial were the number of patients delivered to transplant and overall survival (OS). All end-points were defined according to the revised International Working Group criteria.[12]

All analyses are by intention-to-treat. Categorical end-points [e.g. complete remission (CR) rates] were compared using Mantel–Haenszel tests, giving Peto odds ratios (OR) and confidence intervals (CI). Continuous/scale variables were analysed by non-parametric (Wilcoxon rank sum) tests. Time-to-event outcomes were analysed using the log-rank test, with Kaplan–Meier survival curves. Odds/hazard ratios (OR/HR) less than 1 indicate benefit for the investigational therapy [danorubicin/clofarabine (DClo)] *versus* standard therapy (FLAG-Ida). All survival percentages are at five years unless otherwise stated except for survival censored at transplant where because of lack of follow-up to five years among surviving non-transplanted patients percentages are given at four years. Median follow-up is 46.7 months (range 5.0–68.0 months). Stratified log-rank tests with tests for interaction were performed using the methodology of the Early Breast Cancer Trialists' Collaborative Group[13]

RESULTS

Between November 2009 and December 2012, 94 patients (88 relapsed and six refractory) entered the randomisation, of whom 79 had received initial induction therapy within AML17. The induction that the patients had received within the AML17 trial overall varied over the period of the trial and included ADE (Ara-C/daunorubicin/etoposide) with or without the addition of gemtuzumab ozogamicin (GO) either at a dose of 3 mg/m^2 (GO3) or 6 mg/m^2 (GO6); DA (daunorubicin/Ara-C) with GO3 or GO6, or DA with the daunorubicin dose being 60 mg/m^2 (DA60) or 90 mg/m^2 (DA90).[14,15] For the purposes of this analysis relapsed and refractory patients are combined. A CONSORT diagram for the whole trial is shown in Figure S1. The patients' characteristics and details of prior upfront treatments are given in Table 1; these are well balanced between the arms with 51% of patients in the DClo arm receiving prior GO compared to 59% in the FLAG-Ida arm. Sixty-two patients were allocated to DClo and 32 to FLAG-Ida. The median age of randomised patients was 47years (range 19–63). Of note, 13 (14%) recruited were over 60 years. Only 3/94 patients had adverse-risk cytogenetics reflecting their categorisation as high-risk

TABLE 1 Patient characteristics

	DClo	FLAG-Ida
Number randomised	62	32
Age group (years)		
15–29	8	7
30–39	8	2
40–49	15	8
50–59	22	11
60+	9	4
Gender		
Female	35	16
Male	27	16
Type of disease		
De novo	58	31
Secondary	1	0
High-risk MDS	3	1
Performance status		
0	46	26
1	12	5
2	3	1
3	1	0
4	0	0
Induction treatment		
ADE	12	5
ADE+GO3	7	4
ADE+GO6	7	5
DA+GO3	12	4
DA+GO6	11	6
DA60	5	3
DA90	2	1
Not AML17	6	4
Cytogenetics		
Favourable	9	5
Intermediate	40	19
Adverse	2	1
NK	11	7
FLT3 ITD		
WT	30	17
Mutant	23	10
Not known	9	5
NPM1		
WT	34	18
Mutant	17	7
Not known	11	7
Status of rel/ref		
Relapsed	58	30
Refractory	4	2

Abbreviations: ADE, cytosine arabinoside, daunorubicin and etoposide; AML, acute myeloid leukaemia; DA, daunorubicin and cytosine arabinoside; DClo, daunorubicin/clofarabine; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor with idarubicin; GO, gemtuzumab ozogamicin; ITD, internal tandem duplication; MDS, myelodysplastic syndrome; WT, wild type.

post course 1 and hence ineligibility to re-enter the randomisation at relapse. Thirty-three of the 94 patients had a *FLT3* mutation present at diagnosis but FLT3 status was not determined at relapse. Seventy of the 94 patients (74%) achieved a CR or CR with incomplete bone marrow recovery (CR/CRi) after randomisation. The median time to remission from randomisation was 46 days among remitters, with only 63% of remitters achieving their remission within 60 days of randomisation. Twenty-four patients never achieved a CR or CRi after two courses of induction. The response by treatment allocation for randomised patients is shown in Table 2 and was 74% and 75% for DClo and FLAG-Ida respectively with no significant difference in 30- or 60-day mortality between the arms (6% and 11% for DClo vs 3% and 6% for FLAG-Ida, $p = 0.7$ and 0.8 respectively).

Transplant

Fifty-three patients (57%) received an allogeneic transplant; in addition, nine received a transplant of unknown type; two allografts occurred prior to randomisation (plus one additional transplant of unknown type). Of the remaining 51 allogeneic transplants there were 42 myeloablative transplants (DClo 28 and FLAG-Ida 14;), and nine reduced-intensity transplants (DClo six, FLAG-Ida three). Overall, excluding patients transplanted before randomisation, the rate of allogeneic transplantation did not differ between arms [57% vs 55%; OR 0.81 (0.35–1.90); $p = 0.6$].

The OS at five years from the point of randomisation did not differ for DClo versus FLAG-Ida [21% vs 22%; HR 1.24 (0.76–2.33); $p = 0.4$] (Figure 1A). A test for interaction shows no evidence of heterogeneity of effect by GO upfront ($p = 0.17$) No patient who was not transplanted survived beyond 21months; the HR for survival censored at stem cell transplantation (SCT) was 1.11 (0.52–2.34), $p = 0.8$. When looking at transplantation in the patients who entered remission, there was no significant difference in relapse-free survival (RFS) post transplant (38% vs 29% at four years, HR 1.11 (0.49–2.52); $p = 0.8$) (Table 2).

Stratified analysis of high-risk and relapsed/refractory AML

In total 405 patients in AML17 entered the DClo versus FLAG-Ida randomisation. This included the 311 from the high-risk randomisation post course 1 whose outcome has been previously published[11] and the 94 relapsed/refractory patients reported here. The two groups of patients were combined using standard stratified analytical techniques. The results of the two groups were consistent with each other ($p = 1.0$ between treatment and group). Overall, the whole trial showed a consistent benefit for FLAG-Ida (HR 1.35, CI 1.06–1.73; $p = 0.02$) with no evidence that the relapsed/refractory patients are any different.

TABLE 2 Outcomes of relapsed/refractory randomisation

	DClo	FLAG-Ida	HR/OR, 95% CI	*p*-value
ORR (CR + CRi)	74%	75%	1.04 (0.39–2.76)	0.9
30-days mortality	6%	3%	1.92 (0.30–12.2)	0.5
60-days mortality	11%	6%	1.76 (0.45–6.93)	0.4
5-year OS	21%	22%	1.24 (0.76–2.33)	0.4
4-year OS censored at SCT	0%	0%	1.11 (0.52–2.34)	0.8

Abbreviations: CI, confidence interval; CR/CRi, complete remission /with incomplete bone marrow recovery; DClo, daunorubicin/clofarabine; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor with idarubicin; HR, hazard ratio; OR, odds ratio; ORR, overall response rate; OS, overall survival; SCT, stem cell transplantation.

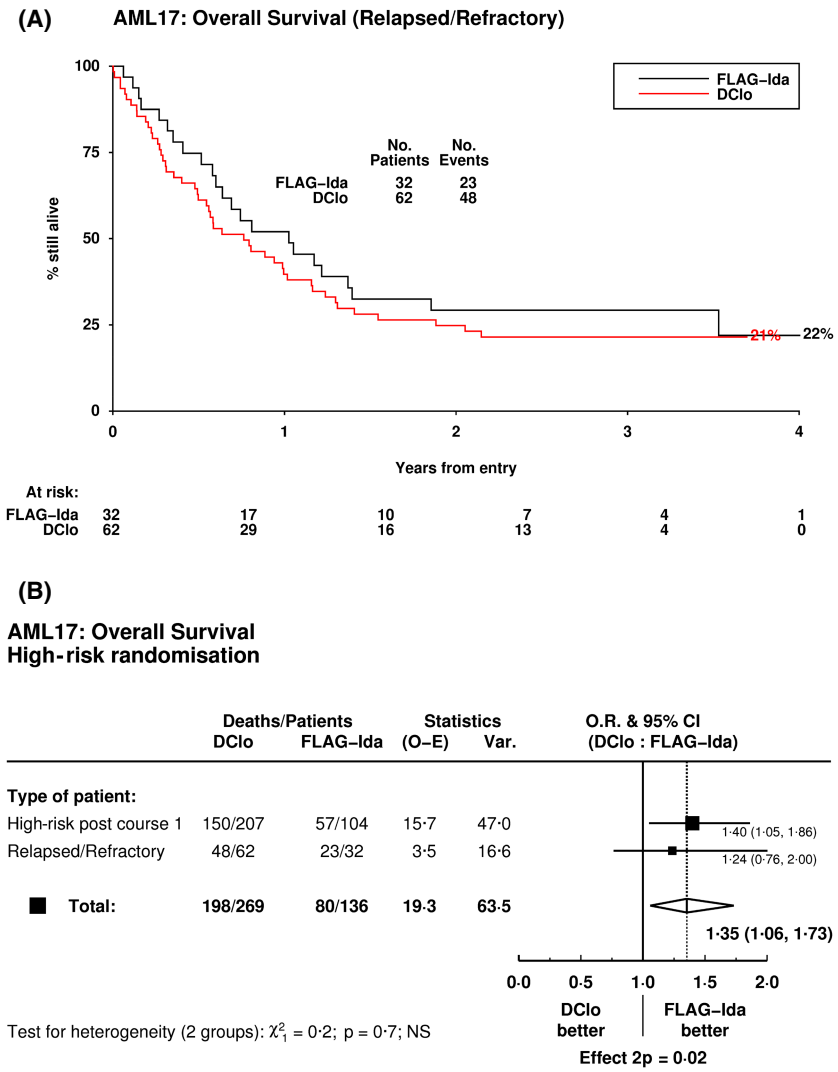

FIGURE 1 (A) Overall survival by randomisation; (B) stratified survival analysis for all high-risk patients [Colour figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

In this trial the aim was to compare a novel salvage regimen against FLAG-Ida and to improve upon the number of patients proceeding to transplant and survival post transplant. In the relapse/refractory patients reported here there was a high overall response rate (CR + CRi) of 74% with no difference between DClo and FLAG-Ida. This unexpectedly high response rate reflects the facts that although the median first remission duration was 10 months and approximately two thirds of patients relapsed after a remission duration of less than one year, nonetheless, 19% of randomised patients had favourable cytogenetics, of whom 93% achieved CR2. This compares with only 1% of patients entering the randomisation having adverse-risk cytogenetics; and only four patients had received a prior

stem cell transplantation. This disposition of patients reflects the trial structure that excluded patients from the relapse randomisation if they had previously been defined as high risk post course 1. Although the total number of patients was relatively small, there was no difference in the proportion of patients in each arm receiving an allogeneic transplant (57% vs 55%). There was no difference in the risk of relapse after transplant and there was no difference in OS between the arms. No patient who was not transplanted survived beyond 21months, which emphasises the importance of transplant in relapsed disease. The disposition of patients entering the randomisation makes comparison with the FLAG-Ida-venetoclax combination problematic as that study included more patients with adverse cytogenetics and prior transplant as well as patients receiving second salvage treatment, although of note, patients with favourable-risk cytogenetics in that study performed less well with FLAG- Ida-venetoclax,[4]

In conclusion, although the FLAG-Ida schedule was not superior in the relapsed setting we previously found it to be so in high-risk patients upfront and a stratified analysis of all patients entering the high-risk randomisation showed overall benefit making it the standard of care for relapsed disease, certainly for patients with favourable or intermediate-risk cytogenetics without a *FLT3* mutation. Whether the combination of FLAG-Ida with venetoclax improves outcome further is a question for future studies.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Conception and design: Alan K. Burnett, Nigel H. Russell and Robert K. Hills. Provision of study materials or patients: Alan K. Burnett, Nigel H. Russell, Richard E. Clark, Sahra Ali, Lars Kjeldsen, Paul Cahalin. Collection and assembly of data: Alan K. Burnett, Robert K. Hills, Nigel H. Russell, Richard E. Clark, Paul Cahalin, Sahra Ali, Lars Kjeldsen, Ian F. Thomas. Data analysis and interpretation: Alan K. Burnett, Robert K. Hills, Nigel H. Russell. Manuscript writing: Nigel H. Russell and Alan K. Burnett drafted the paper which was revised and approved by all authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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