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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Conception and design: AKB. NHR and RKH
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Collection and assembly of data: AKB, RKH, NHR,,RC, PC, SA,OJN IT
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CONFLICT OF INTEREST

The authors declare no competing interests

CLINICAL TRIAL INFORMATION

The study is part of the National Cancer Research Institute (NCRI) Acute Myeloid Leukemia and high-Risk Myelodysplastic Syndrome Trial 17 (Trial Reference ISRCTN 55675535).

Running Title Randomised trial of FLAG-Ida in Relapsed AML

Abstract

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 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 <60 years of age and with mainly favourable or intermediate risk cytogenetics, were randomised to receive up to 3 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 5 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.

Introduction

Patients with relapsed and refractory AML represent an important unmet therapeutic need, for which there is no universally accepted standard of care. ELN guidelines suggest a number of regimens including intermediate dose cytarabine with our without an anthracycline, MEC (mitoxantrone, etoposide and Ara C) or 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 two-fold. 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/G-CSF 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-ß-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 AraC and G-CSF (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 <60 years 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 16+years at trial entry. Relapse of disease which was defined as >5% blasts in the marrow. Patients treated in NCRI trials prior to AML17 who relapsed, could be included. Patients were randomly assigned in a 2:1 ratio to DClo or FLAG-Ida, each for up to 3 courses stratified by baseline information. The intention was that every patient would be eligible to proceed to allogeneic transplant. Consenting patients were randomised (2:1) 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 days 1–5) or FLAG-Ida (fludarabine 30 mg/m^2 days 2–6, ara-C 2 g/m^2 days 2–6, G-CSF 263 µg days 1–7, idarubicin 8 mg/m^2 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 endpoints were defined according to the revised International Working Group criteria (12).

All analyses are by intention-to-treat. Categorical endpoints (e.g. CR rates) were compared using Mantel-Haenszel tests, giving Peto odds ratios and confidence intervals. 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 5 years unless otherwise stated except for survival censored at transplant where because of lack of follow-up to 5 years

among surviving non-transplanted patients percentages are given at 4 years. Median follow up is 46.7 months (range 5.0-68.0 months). Stratified logrank 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 6 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 3mg/m^2 (GO3) or 6mg/m^2 (GO6); DA (daunorubicin/ara-C) with GO3 or GO6, or DA with the daunorubicin dose being 60mg/m^2 (DA60) or 90mg/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 Supplementary figure 1. 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 Gemtuzumab Ozogamicin (GO) compared to 59% in the FLAG-Ida arm. Sixty-two patients were allocated DClo and 32 to FLAG-Ida. The median age of randomised patients was 47 years (range 19-63). Of note 13 (14%) recruited were >60years. Only 3/94 patients had adverse risk cytogenetics reflecting their categorisation as high-risk 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 remission (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 2 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 versus 3% and 6% for FLAG-Ida, p=0.7 and 0.8 respectively).

Transplant: Fifty-three patients (57%) received an allogeneic transplant in addition 9 received a transplant of unknown type; 2 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 9 reduced intensity transplants (DClo 6, FLAG-Ida 3;). 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 5 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 21 months; the hazard ratio for survival censored at 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 RFS post-transplant (38% v 29% at 4 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.

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 1 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 4 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 overall survival between the arms. No patient who was not transplanted survived beyond 21 months, which emphasises the importance of transplant in relapsed disease. The disposition of patients entering the randomisation makes comparison with the FLAG-Ida-Ventoclax 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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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

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**
30d mortality	**6%**	**3%**	**1.92 (0.30-12.2)**	**0.5**
60d mortality	**11%**	**6%**	**1.76 (0.45-6.93)**	**0.4**
5yr OS	**21%**	**22%**	**1.24 (0.76-2.33)**	**0.4**
4yr OS censored at SCT	**0%**	**0%**	**1.11 (0.52-2.34)**	**0.8**

Figure 1a. Overall Survival by Randomisation

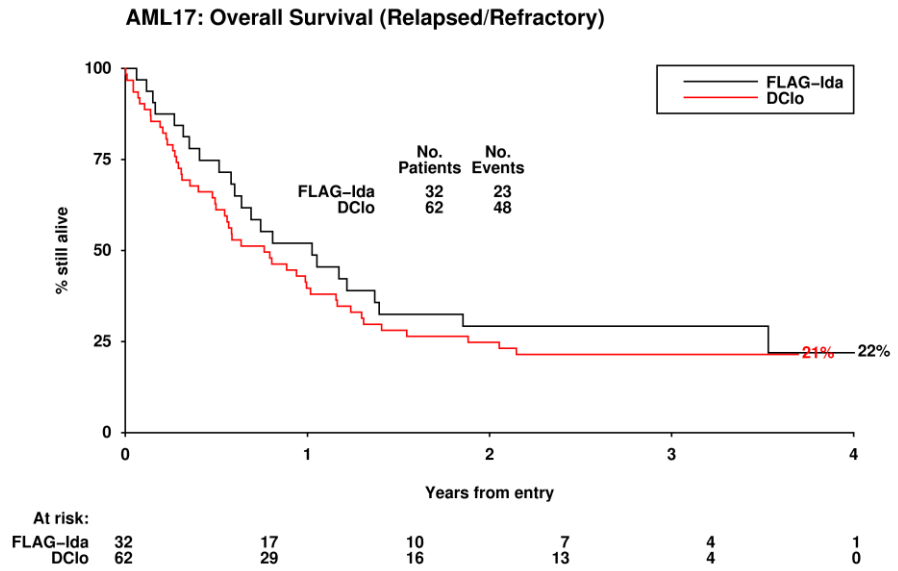

Figure 1b Stratified Survival Analysis for all High Risk Patients