bjh short report

Treatment intensification with FLAG-Ida may improve disease control in younger patients with secondary acute myeloid leukaemia: long-term follow up of the MRC AML15 trial

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Summary

Secondary acute myeloid leukaemia (AML) has a poor outcome following "3 + 7-like" chemotherapy. While CPX-351 has been approved for patients aged 60–75, the optimal treatment, or comparator, in younger patients is less clear. The MRC AML15 trial randomised younger patients between daunorubicin and ara-C (DA) and DA plus etoposide (ADE) and ADE and fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (FLAG-Ida) induction. Overall results failed to show an overall survival benefit for FLAG-Ida despite a reduction in relapse, the outcome of patients <60 years with secondary AML compared to DA/ADE was not reported. In this group (n = 115) response to induction was not different [complete remission/complete remission with incomplete haematological response 81% vs. 79%), however, 5-year overall survival and relapse free survival was superior for FLAG-Ida [37% vs. 27%, stratified hazard ratio (HR) 0·45 (0·33–0·90) P = 0·02 and 41% vs. 22%; stratified HR 0·54 (0·31–0·96) P = 0·04] respectively, suggesting that younger patients with secondary AML may benefit from treatment intensification and that "3 + 7" may not be the optimal comparator in trials for this group of patients.

Keywords: secondary acute myeloid leukaemia, chemotherapy, clinical trial.

Introduction

Patients with secondary acute myeloid leukaemia (AML) have a poor outcome with intensive "3 + 7" chemotherapy, or equivalent, with a high risk of relapse.[1–3] This is partly due to a high incidence of adverse cytogenetics and genetic abnormalities, including mutations of *TP53,* which are found particularly in therapy-related cases.[4] A recent phase 3 trial of CPX-351, a novel liposomal encapsulation of daunorubicin and ara-C (DA), found significant survival benefit compared to standard DA "3 + 7" chemotherapy in a secondary AML population aged 60–75 years (median 67 years) with a history of prior myelodysplastic syndrome (MDS) or chronic myelomonocytic leukaemia, therapy-related AML, or an MDS-related karyotype [median overall survival (OS) 9·6 vs. 6·0 months P = 0·005] and with a performance status (PS) of 0-2. CPX-351 has become the standard of care in this population and age group.[5] However, there are no similar data in younger patients where it is unclear whether DA is an appropriate comparator for these patients or whether they do better with more intensive chemotherapy such as fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor (FLAG-Ida). In the UK MRC AML15 trial, FLAG-Ida resulted in a significant reduction in the risk of relapse and improved relapse-free survival (RFS), but with increased myelosuppression compared to DA plus etoposide (ADE) chemotherapy. In a randomised comparison, this was equivalent to DA with respect to relapse risk, deaths in remission, RFS and OS.[6] There were more deaths in remission with FLAG-Ida, resulting in no OS advantage compared to ADE, either overall or in any subgroup.[6] The outcome of secondary AML with FLAG-Ida was, however, not compared to DA/ADE combined. As secondary AML patients are generally more chemoresistant than *de novo* patients, we considered that they might benefit from more intensified therapy. In the current analysis, we evaluated the long-term outcome of secondary AML in patients aged 16–59 who fulfilled the other eligibility criteria for the CPX-351 trial and who enrolled in the MRC AML15 trial between 2002 and 2009.

Patients and Methods

Of the 1736 patients aged 16–59, randomised in the AML15 trial, 115 (6·6%) had secondary AML defined as AML

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secondary to previous chemotherapy/radiotherapy, or a prior haematological disorder, including myelodysplastic syndrome (MDS), with a PS of 0–2. Patients were initially randomised to two courses of DA, ADE or FLAG-Ida, the details of the treatment given and the outcomes have previously been published.[6] Briefly, DA 3 + 10 chemotherapy comprised DA 50 mg/m^2 days 1, 3, 5 and cytarabine 100 mg/m^2 days 1–10 every 12 h. DA 3 + 8 comprised DA 50 mg/m^2 days 1, 3, 5 and cytarabine 100 mg/m^2 days 1–8 every 12 h. ADE added etoposide to DA, 100 mg/m^2 days 1–5. FLAG-Ida comprised fludarabine 30 mg/m^2 i.v. on days 2–6 inclusive, cytarabine 2 g/m^2 over 4 h starting 4 hours after fludarabine on days 2–6, G-CSF (lenograstim 263 μg [1 vial]) subcutaneous daily on days 1–7; idarubicin 8 mg/m^2 i.v. daily on days 4–6. Patients could be randomly assigned to a single dose of gemtuzumab ozogamicin (3 mg/m^2) in induction course 1.[7] The trial was approved by the Wales Multicentre Research Ethics Committee 3 and each institution's ethical committee, in accordance with the Declaration of Helsinki.

Survival was evaluated using the Kaplan–Meier method and compared using stratified log-rank tests and Cox regression for multivariate analyses. Median follow-up was 115·6 months (range 8·4–145·2). Outcomes are reported at 5 years. An odds ratio (OR) or hazard ratio (HR) of <1 indicates better outcomes for FLAG-Ida. Analyses are presented as both unadjusted and after adjustment for the cytogenetic risk group. For this analysis, the outcomes for patients receiving DA and ADE in AML15 were combined.

Results

Of the 115 patients with secondary AML, 73 received DA or ADE and 42 received FLAG-Ida. Only eight patients received gemtuzumab, five with DA/ADE and three with FLAG-Ida. Patient characteristics are detailed in Table I. Median age was 52 years (range 16–59); 52% were male; median white blood cell count was 6.4 × 10^9/L (range 0·2–260·0); 10%, 65% and 25% had a favourable, intermediate and adverse karyotype respectively. There was some evidence that patients given FLAG-Ida had a worse risk karyotype (P = 0·10). The complete remission/complete remission with incomplete haematological response rate was 80% [DA/ADE 79%, FLAG-Ida 81%, unadjusted OR [95% confidence interval (CI)] 0·91 (0·35–2·34) P = 0·8; stratified OR 0·54 (0·19–1·55) P = 0·3]. Five-year survival was better for patients treated with FLAG-Ida (37% for FLAG-Ida vs. 27% for DA/ADE, unadjusted HR 0·81 (0·52–1·26) P = 0·4) (Fig 1, Table II). This was significant in analyses adjusted for imbalances in cytogenetics [stratified HR 0·45 (0·33–0·90) P = 0·02]. FLAG-Ida significantly reduced relapse [35% for FLAG-Ida vs. 64% for DA/ADE, stratified HR 0·47 (0·24-0·93) P = 0·03]; (Table II), without evidence of significant excess mortality in remission [24% vs. 14% for DA/ADE, stratified HR 0·79 (0·26–2·34) P = 0·7]. RFS was improved with FLAG-Ida after adjustment [41% vs. 22%; unadjusted HR 0·70 (0·43-1·15) P = 0·16; stratified HR 0·54 (0·31-0·96) P = 0·04] (Table II). In a multivariable analysis of RFS, only the cytogenetic group [HR 2·06 (1·21-3·51) P = 0·03] and FLAG-Ida [HR 0·52 (0·29-0·95) P = 0·03] emerged as a significant prognostic factors. Allografts in first complete remission occurred in 24% of cases (31% for FLAG-Ida vs. 21% for DA/ADE P = 0·2) The survival benefit for FLAG-Ida [HR 0·49 (0·26-0·90) P = 0·02] was consistent with the overall result when survival was censored at the time of transplant (Table II). As such, there is no evidence to conclude that the effect seen here was due to transplantation. In a landmark analysis at 120 days post-remission, survival in the transplanted group was better than the non-transplanted group after adjustment for cytogenetics [43% vs. 32%, unadjusted HR 0·80 (0·45-1·44) P = 0·3, stratified HR 0·48 (0·23–0·98) P = 0·04].

Table I. Demographics of patients with secondary AML randomised between DA/ADE and FLAG-Ida.

	Overall	FLAG-Ida	DA/ADE	*P*
Number of patients	115	42	73	
Median age (years) (range)	52 (18–59)	51·5 (18–59)	52 (32–59)	0·96
Male *n* (%)	60 (52)	21 (50)	39 (53)	0·7
Median WBC (x10^9/L) range		5·2 (0·2–260·0)	6·9 (0·6–197·0)	>0·99
Cytogenetics *n* (%)				0·10
Favourable	9 (10)	2 (6)	7 (13)	
Intermediate	59 (65)	22 (61)	37 (67)	
Adverse	23 (25)	12 (33)	11 (20)	
Missing	24	6	18	
WHO/ECOG Performance Status *n* (%)				0·6
0	79 (69)	28 (67)	51 (70)	
1	35 (30)	13 (31)	22 (30)	
2	1 (1)	1 (2)	0	

DA, daunorubicin and ara-C; ADE, DA plus etoposide; FLAG-Ida, fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor.

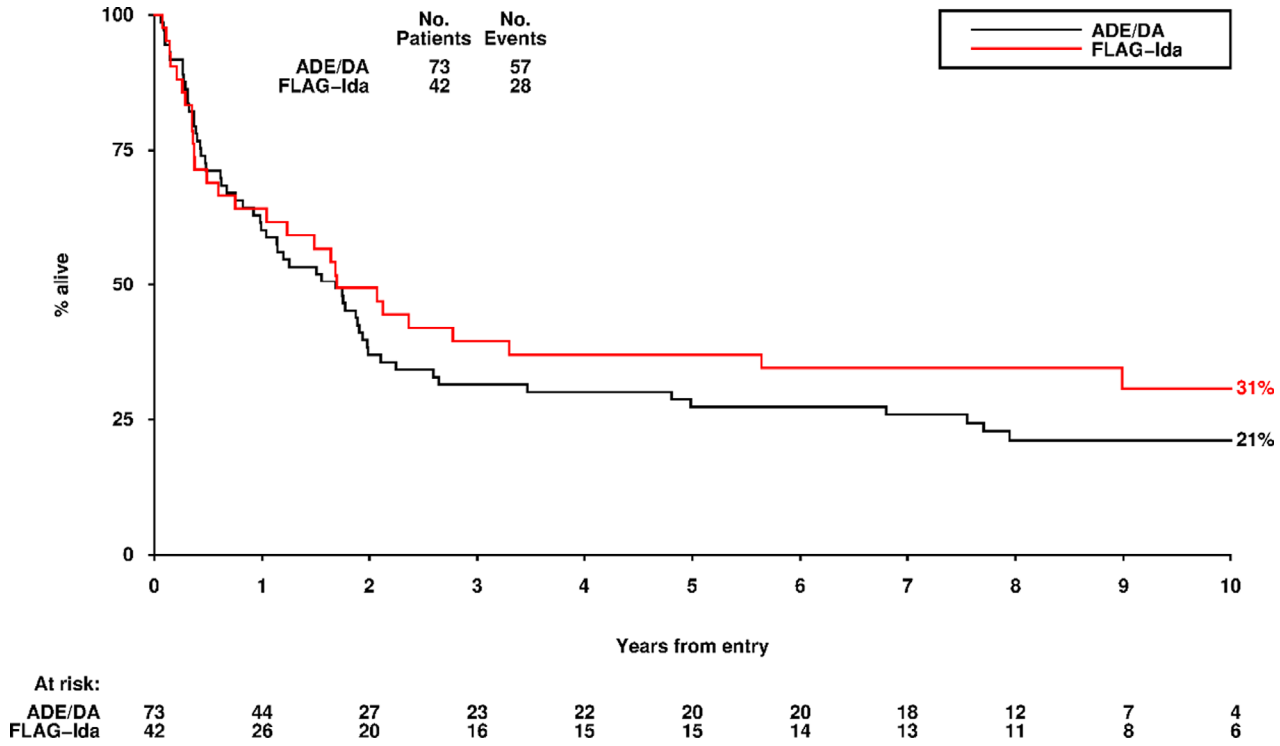

Fig 1. Overall survival for patients with secondary AML randomised between FLAG-Ida and DA/ADE. DA, daunorubicin and ara-C; ADE, DA plus etoposide; FLAG-Ida, fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor. [Colour figure can be viewed at wileyonlinelibrary.com]

Table II. Outcomes of patients by allocated treatment.

	FLAG-Ida, %	DA/ADE, %	Unadjusted OR/HR (95% CI)	Stratified OR/HR (95% CI)
CR/CRi	81	79	0·91 (0·35–2·34); $P = 0·8$	0·54 (0·19–1·55); $P = 0·3$
5-year cumulative incidence of relapse	3	64	0·56 (0·32–1·00); $P = 0·05$	0·47 (0·24–0·93); $P = 0·03$
5-year cumulative incidence of death in remission	24	14	1·32 (0·50–3·50); $P = 0·6$	0·79 (0·26–2·34); $P = 0·7$
5-year relapse-free survival	41	22	0·70 (0·43–1·15); $P = 0·16$	0·54 (0·31–0·96); $P = 0·04$
2-year survival from relapse	8	19	1·43 (0·71–2·89); $P = 0·3$	0·67 (0·29–1·55); $P = 0·3$
5-year overall survival	37	27	0·81 (0·52–1·26); $P = 0·4$	0·45 (0·33–0·90); $P = 0·02$
5-year survival censored at SCT	54	39	0·77 (0·45–1·33); $P = 0·3$	0·49 (0·26–0·90); $P = 0·02$
Median survival	20.6 months	20.2 months		

AML, acute myeloid leukaemia; CR/CRi, complete remission/complete remission with incomplete haematological response; DA, daunorubicin and ara-C; ADE, DA plus etoposide; FLAG-Ida, fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor; OR. Odds ratio; HR, hazard ratio; SCT, stem cell transplant.

Conclusion

Outcomes in younger patients with secondary AML are poor with DA/ADE chemotherapy, with a median OS of 20·2 months and 5-year and 1- year survival of 27% and 21% respectively. Despite a similar median OS (20·6 months), FLAG-Ida showed a significant improvement in survival in analyses after adjustment for the imbalance in the cytogenetic risk group, with 5- and 10-year survival of 37% and 31% respectively. While numbers are small, and a greater number of patients received an allograft in first remission in the FLAG-Ida arm than in the DA/ADE group, there is a suggestion that recipients of an allograft had better outcomes after adjustment for cytogenetic risk, findings consistent with outcomes of previous reports of allogeneic transplant in secondary AML.[8,9] The benefit seen with FLAG-Ida was due to a significant reduction in the risk of relapse, without a significant increase in the cumulative incidence of death in remission. Furthermore, the survival benefit for FLAG-Ida was seen when survival was censored at the time of transplant. Interestingly, the OS benefit for FLAG-Ida only emerged after 2 years and demonstrates the need for long-term follow-up when considering questions of induction treatment intensification. To summarise, these results are exploratory and cannot be

regarded as definitive but suggest that "3 + 7" may not be an appropriate standard of care in younger patients with secondary AML and that FLAG-Ida would be an appropriate comparator for future prospective trials in this younger population. We have previously reported improved survival with FLAG-Ida treatment as treatment intensification for younger patients identified with high risk AML following induction therapy.[10] Here we extend these observations to another high risk group of patients, those with secondary AML. The ongoing NCRI AML19 (ISRCTN78449203) trial is currently randomising CPX-351 *versus* FLAG-Ida in patients aged <60 years with high risk AML.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Author contributions

NHR and RH designed the study and analysed the data. AKB and NR were principal investigators of the trial. NHR, AKB, LK and MD provided data. NHR and RH wrote the manuscript. All authors read and approved the final manuscript.

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