bjh short report

Therapy for isocitrate dehydrogenase 2 (*IDH2*)^{R172}-mutant acute myeloid leukaemia

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Summary

Although we earlier reported a very poor outcome for younger adult patients with isocitrate dehydrogenase 2 (*IDH2*)^{R172}-mutated acute myeloid leukaemia (AML) entered into UK trials compared to *IDH2*^{WT} and *IDH2*^{R140}-mutated patients, this was not corroborated by a study from the German-Austrian AML Study Group. We have therefore investigated a later cohort of *IDH2*-mutated patients to identify any changes in outcome and whether this could inform the optimal treatment for *IDH2*^{R172} AML. We found an improved outcome for *IDH2*^{R172}-mutated AML in the later trials and the data suggests that this may be due to the increased use of allogeneic transplantation to consolidate first remission.

Keywords: acute myeloid leukaemia, isocitrate dehydrogenase 2 (*IDH2*)^{R172} mutations, prognostic impact, optimal therapy, allogeneic transplantation.

Introduction

Mutations in the isocitrate dehydrogenase 2 (*IDH2*) gene are found in ~10% of adult cases of acute myeloid leukaemia (AML),[1–3] occurring at either residue R140 or R172. In a study of younger adult patients entered into the UK Medical Research Council (MRC) AML10 and AML12 [International Standard Randomised Controlled Trial Number (ISRCTN) 17833622] trials between 1988 and 2002, we found that the two mutations were associated with different disease biology.[3] Overall, 92% of *IDH2*-mutated patients (*IDH2*^{MUT}) had intermediate-risk cytogenetics, with normal cytogenetics predominating in *IDH2*^{R140} and abnormal cytogenetics in *IDH2*^{R172}. *IDH2*^{R172} patients generally presented with significantly lower white blood cell counts (WBC), and were much less likely to have FMS-like tyrosine kinase 3 (*FLT3*) or nucleophosmin 1 (*NPM1*) mutations. This difference in biology was confirmed in the cohort studied by Papaemmanuil *et al.*[2] and, although rare, they designated *IDH2*^{R172} AML as a separate disease entity. We also noted that, compared to patients with *IDH2* wild-type (*IDH2*^{WT}) disease, *IDH2*^{R140} patients tended to have a better outcome and *IDH2*^{R172} patients a worse outcome, the difference in the cumulative incidence of relapse (CIR) and overall survival (OS) between the two mutation sites being highly significant ($P = 0{\cdot}0001$ and $P = 0{\cdot}0002$ respectively). The poor survival in *IDH2*^{R172} patients (9% at 10 years) was similar to those with adverse cytogenetics,[3] and was in accord with some previous studies,[4,5] but was not corroborated by the Papaemmanuil *et al.*[2] study. We have therefore investigated *IDH2* mutational status in a later cohort of UK patients with intermediate-risk AML entered into the MRC AML15 (ISRCTN17161961) and UK National Cancer Research Institute (NCRI) AML17 (ISRCTN55675535) trials between 2002 and 2014[6,7] to see if our earlier findings still pertained, to understand the reason for any change that may have occurred, and to provide insights into the optimal treatment of *IDH2*^{R172} AML. We found that outcome of *IDH2*^{R172} patients was improved in the later AML15 and AML17 trials and suggest that this is due to the increased use of allogeneic transplantation to consolidate first remission (CR1).

Patients and methods

The study cohort from AML10 and AML12 are as described previously with the present analysis restricted to the patients

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with intermediate-risk cytogenetics ($n = 910$).[3] The cohort from AML15 and AML17 ($n = 1204$) excluded patients with high-risk myelodysplastic syndrome, as such patients were not entered into AML10 and AML12. Informed patient consent was obtained in accordance with the Declaration of Helsinki; ethical approval for tissue use from the Wales Research Ethics Committee 3. Over the time period of these trials there was a progressive improvement in OS but no significant differences were observed between the different induction chemotherapy regimens.[8] Mutation detection and statistical analyses were as described previously.[3]

Results and discussion

Demographics of all the *IDH2*-genotyped patients studied here are shown in Table SI. Of note, the later AML15+17 cohort were significantly older than the earlier AML10+12 cohort (median ages 50 vs. 43 years respectively, $P < 0{\cdot}0001$) due to two main factors. The recommended upper age limit in the AML10 trial was 55 years and subsequently increased to 60 years in later trials. Furthermore, the upper age limit was a recommendation only and older patients could be entered into the trials if considered fit enough for intensive therapy. The proportion of patients aged >60 years increased progressively from <0·5% in AML10 to 3% in AML12, 13% in AML15 and 26% in AML17. Despite this increase in age, there was a marked improvement in performance status at the time of diagnosis and a fall in the presenting WBC, both factors possibly due to earlier diagnosis. There was also a significant increase in the use allogeneic transplantation as consolidation of CR1 in the later trials (13% vs. 23% in the two cohorts respectively, $P < 0{\cdot}0001$). There was a similar trend ($P = 0{\cdot}06$) if the analysis was restricted to $IDH2^{MUT}$ patients. The incidence of a normal karyotype, an *IDH2* mutation or a $FLT3^{ITD}$ did not differ over time, but there was a decrease in the incidence of an *NPM1* mutation (50% vs. 42%, $P = 0{\cdot}0002$), in line with the known reduced frequency of *NPM1* mutations in older patients.[9]

The *IDH2* mutation frequency was similar in the AML15+17 and AML10+12 cohorts, 13·6% *versus* 12·6% respectively ($P = 0{\cdot}5$); with 72% $IDH2^{R140}$ and 28% $IDH2^{R172}$ *versus* 78% and 22% ($P = 0{\cdot}3$) (Table SI). In both cohorts $IDH2^{MUT}$ were older than $IDH2^{WT}$ patients, and $IDH2^{R172}$ were slightly older than $IDH2^{R140}$ patients (P for trend 0·04 and <0·0001 in AML10+12 and AML15+17 respectively) (Table I). $IDH2^{R172}$ and $IDH2^{R140}$ disease characteristics were also very similar including lower median presenting WBC in $IDH2^{R172}$ than $IDH2^{R140}$ or $IDH2^{WT}$ ($P < 0{\cdot}0001$ for both cohorts), and significantly lower incidence of a normal karyotype in $IDH2^{R172}$ than $IDH2^{R140}$ or $IDH2^{WT}$ (P for trend 0·01 in both cohorts). Combining the two cohorts, the difference in karyotype between $IDH2^{R140}$ and $IDH2^{R172}$ disease was highly significant ($P = 0{\cdot}0004$). In those cases with abnormal cytogenetics, the most frequent abnormality was trisomy 8, which was similar in $IDH2^{WT}$, $IDH2^{R140}$ and $IDH2^{R172}$ (23%, 32% and 27%, $P = 0{\cdot}6$) and did not differ significantly between cohorts. Trisomy 11 was rare in the $IDH2^{WT}$ cases (1%) but was significantly more frequent (17%) in those cases with an *IDH2* mutation ($P = 0{\cdot}01$). It was significantly more common in cases with an $IDH2^{R172}$ mutation (33% vs. 6% for $IDH2^{R140}$; $P = 0{\cdot}01$). In both cohorts, $FLT3^{ITD}$ frequency was significantly lower in $IDH2^{R172}$ than $IDH2^{R140}$ patients [4% and 20% respectively in AML10+12 ($P = 0{\cdot}0005$), 7% and 32% in AML15+17 ($P = 0{\cdot}01$)] and $NPM1^{MUT}$ was almost mutually exclusive with an $IDH2^{R172}$ mutation. No cases with concomitant $NPM1^{MUT}$ and $IDH2^{R172}$ were detected in AML15+17 and only one case in AML10+12 (P value for difference from $IDH2^{R140}$ <0·0001 in both cohorts). These results confirm that $IDH2^{R172}$ disease is a biologically distinct leukaemic entity. They suggest that the biochemical change(s) induced by the R172 mutation may be quantitatively or qualitatively different from that of the R140 mutation and require fewer co-operative mutations to induce frank leukaemia, or that the R140 and R172 mutations have different causality, which is in accord with the higher frequency of an abnormal karyotype in R172 disease.

Regarding outcome, the CR1 rate was lowest in $IDH2^{R172}$ patients in both cohorts but not significantly different from $IDH2^{WT}$ (Table I). In the combined cohort, there was a trend towards a lower remission rate in $IDH2^{R172}$ compared to $IDH2^{R140}$ ($P = 0{\cdot}1$). The CIR at 5 years in $IDH2^{R172}$ patients was more than twice that in $IDH2^{R140}$ patients in AML10+12 (65% vs. 29%, $P = 0{\cdot}01$), but this difference was not seen in the AML15+17 cohort (43% vs. 40%, $P = 0{\cdot}2$). In accord with this, OS was significantly less in $IDH2^{R172}$ compared to $IDH2^{R140}$ patients in AML10+12 (25% vs. 56% at 5 years, $P = 0{\cdot}01$) (Fig 1A) whereas in AML15+17, although OS was still less at 5 years in $IDH2^{R172}$ compared to $IDH2^{R140}$ patients, the difference was less marked (38% vs. 52%, $P = 0{\cdot}3$) (Fig 1B,C). This was predominantly due to an improvement in the outcome of $IDH2^{R172}$ patients and raised the possibility that there had been a mutation-specific improvement in outcome in response to changing therapy.

Two therapeutic changes were considered. Firstly, some AML15+17 patients were treated with the anti-CD33 antibody, Mylotarg.[6,7] However, it was only given to eight of 69 $IDH2^{R172}$ patients and, although numbers were too few for formal analysis, there was no suggestion that Mylotarg had improved the outcome. A second possibility was the increased use of allogeneic transplantation to consolidate CR1. In AML10+12, 11 of 90 $IDH2^{R140}$ patients (12%) had a CR1 allograft and seven of them were alive at 5 years (64%); five of 25 $IDH2^{R172}$ patients (20%) had a CR1 allograft and three were alive at 5 years (60%). In the 79 $IDH2^{R140}$ patients who did not receive an allograft, 43 (54%) were still alive at 5 years, which is equivalent to the transplanted patients when one takes into account that the non-transplanted group includes those patients who did not achieve CR. Of the 20 $IDH2^{R172}$ patients who did not receive

Table I. Characteristics and outcome of patients according to isocitrate dehydrogenase 2 (*IDH2*) genotype.

Characteristic	AML10+12 cohort (n = 910)				AML15+17 cohort (n = 1204)			
IDH2 genotype	WT	R140	R172	*P*	WT	R140	R172	*P*
Age, years, median (range)	43 (16–68)	47 (20–60)	49 (29–62)	0·004	50 (16–74)	54 (18–68)	57 (31–70)	<0·0001
Sex, male, %	47	50	68	0·1	51	58	55	0·3
Disease type				0·5				0·6
Secondary AML, %	7	9	12		7	9	5	
WBC, $\times 10^9$/l, median (range)	28·0 (0·4–480)	24·4 (1·0–365)	3·9 (0·6–150)	<0·0001	15·9 (0·3–355)	18·0 (0·2–319)	2·2 (0·3–456)	<0·0001
Cytogenetics*, %				0·008				0·01
Normal karyotype	66	73	40		66	78	55	
Abnormal karyotype	34	27	60		34	22	45	
FLT3^{ITD}, *n* (%)				0·0005				0·01
WT	533 (67)	72 (80)	24 (96)		741 (71)	87 (73)	41 (93)	
Mutant	262 (33)	18 (20)	1 (4)		299 (29)	32 (27)	3 (7)	
Unknown	0	0	0		0	1	0	
NPM1, *n* (%)				<0·0001				<0·0001
WT	469 (51)	20 (22)	84 (96)		599 (58)	54 (45)	44 (100)	
Mutant	386 (49)	70 (78)	1 (4)		440 (42)	65 (53)	0	
Unknown	0	0	0		1	1	0	
CR + CRi rate, %	87	91	80	0·3	88	87	82	0·5
CIR, %				0·01				0·2
@ 5 years	51	29	65		49	40	43	
@ 10 years	52	39	65		50	41	43	
OS, %				0·01				0·3
@ 5 years	38	56	25		44	53	38	
@ 10 years	34	43	11		37	49	33	
Allograft in CR1, *n* (%)	102 (13)	11 (12)	5 (20)	0·6	240 (23)	22 (18)	15 (34)	0·1

CIR, cumulative incidence of relapse; CR, complete remission; CR1, first complete remission; CRi, complete remission with incomplete hematological recovery; *FLT3*^{ITD}, FMS-like tyrosine kinase 3-internal tandem duplication; *NPM1*, nucleophosmin 1; OS, overall survival; WT, wild-type.

*All patients had intermediate-risk cytogenetics.

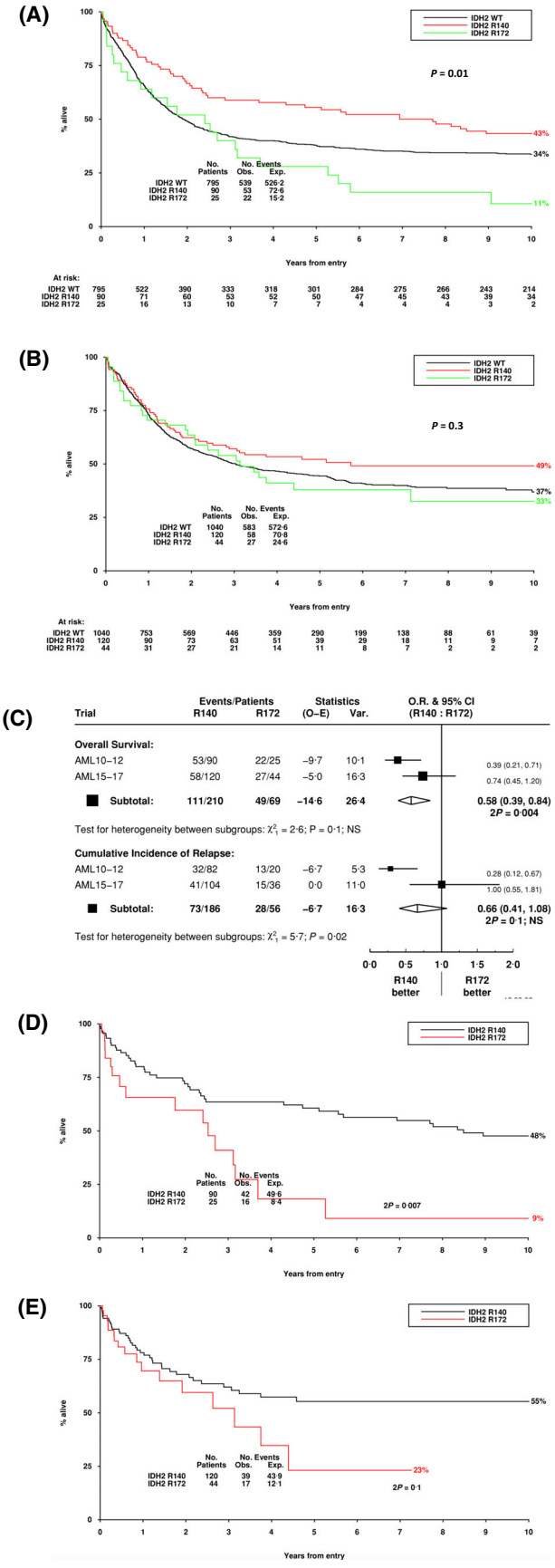

Fig 1. Comparison of outcome stratified according to isocitrate dehydrogenase 2 (*IDH2*) mutant status in the two different trial cohorts. Kaplan–Meier curves for overall survival (OS) in (A) the acute myeloid leukaemia (AML)10+12 and (B) the AML15+17 cohorts. (C) Forest plot for mutant impact on OS stratified according to trial cohort. (D) Kaplan–Meier curves for OS censored at allograft in first complete remission (CR1) in the AML10+12 and (E) the AML15+17 cohorts. [Colour figure can be viewed at wileyonlinelibrary.com]

an allograft, only four (20%) were alive at 5 years. In AML15+17, 22 of 120 *IDH2*^{R140} patients (18%) had a CR1 allograft and eight of 18 with long enough follow-up were alive at 5 years (44%). In those not receiving a CR1 allograft, the proportion of patients alive at 5 years was again similar (31 of 77, 40%). In *IDH2*^{R172} patients, 15 of 44 (34%) received a CR1 allograft and nine of 13 with adequate follow-up (69%) were alive at 5 years; 29 did not receive an allograft and only two of 24 (8%) with adequate follow-up were alive at 5 years. These data raise the possibility that *IDH2*^{R172} patients fare as well as *IDH2*^{R140} patients if they are allografted in CR1 but more poorly if remission is not consolidated in this way. To illustrate this further, the survival curves for *IDH2*^{R140} and *IDH2*^{R172} patients are shown in Fig 1D,E for both cohorts with censoring of patients at the time of transplantation. In AML10+12, OS censored for allogeneic transplantation was 63% at 5 years in those with *IDH2*^{R140} disease and 20% in those with *IDH2*^{R172} disease (P = 0·01), whereas in AML15+17, it was 48% in *IDH2*^{R140} disease and 19% in *IDH2*^{R172} disease (P = 0·1).

There is controversy over whether CR1 in younger adult patients with intermediate-risk cytogenetics should be consolidated with an allogeneic transplant or whether such an intensive approach should be reserved for those who relapse and then achieve a second remission.[10–12] For rare subtypes such as *IDH2*^{R172} AML, it is even more difficult to make an evidence-based judgement and caution should be exercised in making definitive statements about optimal treatment. Despite these limitations, the present data raises the possibility that *IDH2*^{R172} patients have better outcomes if their CR1 is consolidated with an allogeneic transplant and we suggest that this should be considered as part of their treatment strategy. However, we also note that encouraging early results have been reported with the IDH2 inhibitor enasidenib in both *IDH2*^{R140} and *IDH2*^{R172} disease, and whether or not consolidation of CR1 with an allogeneic transplant will still be required in cases with an *IDH2*^{R172} mutation is not yet known.[13]

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Author contributions

David C. Linch designed the study; Rosemary E. Gale provided genotyping data; David C. Linch, Rosemary E. Gale and Robert K. Hills analysed the data; Alan K. Burnett and Nigel Russell were principal trial co-ordinators and provided data; David C. Linch and Rosemary E. Gale wrote the manuscript; all authors reviewed the manuscript.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Demographics of the isocitrate dehydrogenase 2 (*IDH2*)-genotyped patients included in the study.

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