Impact of new treatment guidelines pertaining to the indication for allogeneic stem cell transplantation in intermediate-risk acute myeloid leukaemia at Ghent University Hospital: A retrospective analysis

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SUMMARY

Since several years, it has become clear that intermediate-risk acute myeloid leukaemia patients in an acceptable clinical condition can benefit from allogeneic stem cell transplantation thanks to the improvement in relapse free survival. This study retrospectively analysed the outcome of all intermediate-risk acute myeloid leukaemia patients treated with intensive chemotherapy at the Ghent University Hospital between 01-01-2013 and 30-04-2017 in an effort to determine the impact of a new in-hospital treatment guideline adopted in April 2015. This guideline recommends all intermediate-risk acute myeloid leukaemia patients who are fit for intensive therapy to proceed to allogeneic stem cell transplantation in first complete remission. Unfortunately, we could not demonstrate an improvement in the relapse free survival after implementation of the treatment guideline. Nevertheless, exploratory analysis of the entire group suggests a survival benefit from allogeneic stem cell transplantation, with significantly improved relapse free survival and a trend towards a better overall survival.
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INTRODUCTION

The optimal post remission treatment in patients with acute myeloid leukaemia (AML) should be individually tailored, according to the estimated relapse risk, performance status and expected treatment morbidity and mortality. As of yet, there is no universally accepted strategy in intermediate-risk (IR) patients regarding the use of allogeneic stem cell transplantation (SCT), and studies are still ongoing to determine the optimal post-remission treatment in this patient subset. Since several years, it has become clear that allogeneic SCT can reduce the risk of relapse in IR AML patients in acceptable clinical condition. However, the gain in relapse reduction attributable to the graft-versus-leukaemia effect of an allograft can be offset against the treatment related mortality.[1-4] In April 2015, the Ghent University Hospital introduced a new in-hospital treatment guideline that recommends all IR AML patients who are eligible for intensive treatment to proceed to consolidation with allogeneic SCT if a suitable related or unrelated donor is available.

METHODS

This study retrospectively analysed the outcome of all IR AML patients (based on the 2017 European LeukemiaNet [ELN] criteria) treated with intensive chemotherapy at the Ghent

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Keywords: acute myeloid leukaemia, haematopoietic stem cell transplantation.

TABLE 1. Baseline characteristics: intermediate-risk patients treated with intensive chemotherapy (N=43).

Variable	Cohort 1 (N=17) N(%) - Median (IQR)	Cohort 2 (N=26) N(%) - Median (IQR)	p
Age (years)	63 (55.5-61.5)	50.5 (33.5-62.3)	0.009
WBC count (/μL)	4350 (1725-70450)	31640 (3355-93800)	0.130
WBC count			0.043
0-10000	12 (70.6)	9 (34.6)	
10001-50000	1 (5.9)	7 (26.9)	
50001-100000	0 (0)	5 (19.2)	
>100000	4 (23.5)	5 (19.2)	
BM blast count (%)	40.6 (32.3-76.1)	48.5 (27.3-66.1)	0.743
WHO classification			0.066
Recurrent cytogenetic abnormalities	2 (11.8)	9 (34.6)	
AML-MRC	9 (52.9)	4 (15.4)	
t-AML	2 (11.8)	3 (11.5)	
AML-NOS	3 (17.6)	9 (34.6)	
Ambiguous lineage	1 (5.9)	1 (3.8)	
alloSCT in CR1	4 (23.5)	17 (65.4)	0.012
Disease status pre-SCT			0.190
Active disease	1 (25)	0 (0)	
CR1	3 (75)	17 (100)	
CR after 2nd cycle	11 (84.6)	19 (95.0)	0.547
Relapse			0.110
No	7 (41.2)	18 (69.2)	
Primary refractory	3 (17.6)	1 (3.8)	
Relapse > 6M, no SCT	4 (23.5)	1 (3.8)	
Relapse < 6M, no SCT	2 (11.8)	3 (11.5)	
Relapse < 6M after SCT	0 (0)	0 (0)	
Relapse > 6M after SCT	1 (5.9)	3 (11.5)	
Mortality	10 (58.8)	13 (50.0)	0.756

IQR: interquartile range, WBC: white blood cell, BM: bone marrow, WHO: World Health Organization, AML: acute myeloid leukaemia, MRC: myelodysplasia-related changes, t-AML: therapy related AML, NOS: not otherwise specified, alloSCT: allogeneic stem cell transplantation, CR1: first complete remission, M: months.

University Hospital between 01-01-2013 and 30-04-2017.[3] Patients with acute promyelocytic leukaemia were excluded from the analysis.

Patients were divided into two cohorts: those treated according to previous hospital guidelines (cohort 1, diagnosed between January 2013 and December 2014) and those treated according to the new in-hospital guidelines (cohort 2, diagnosed between January 2015 and April 2017). Baseline patient characteristics are shown in *Table 1*.

The primary endpoint was a difference in relapse free survival (RFS). RFS was defined as time from first complete remission (CR1) until occurrence of relapse or death from any cause. Overall survival (OS) was defined as the time from diagnosis until death from any cause or until the time

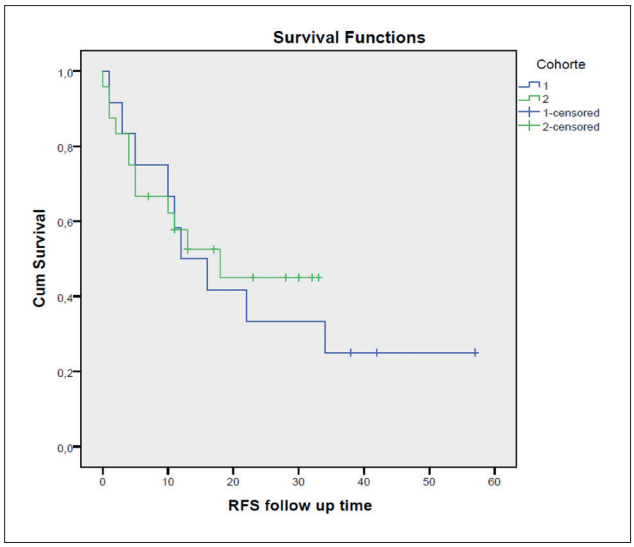

FIGURE 1. Comparison of RFS (in months) between both patient cohorts. Cohort 1 median RFS twelve months. Cohort 2 median RFS eighteen months. p=0.747.
(1=Cohort 1, 2=Cohort 2).

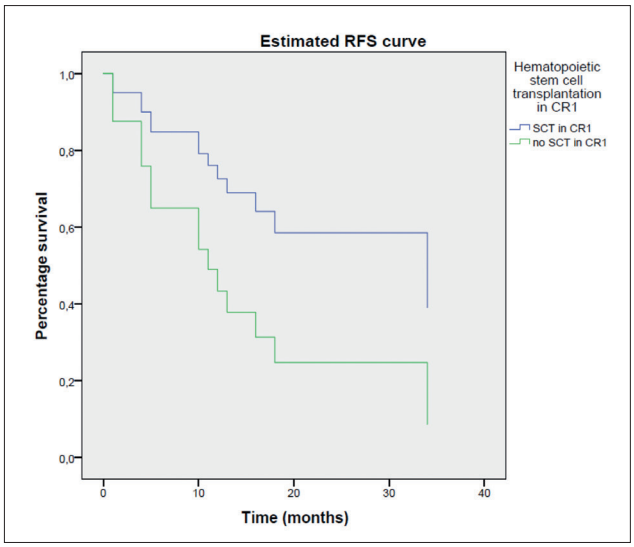

FIGURE 2. Impact of allogeneic SCT in CR1 on RFS independent of age. HR 0.388, p=0.047.

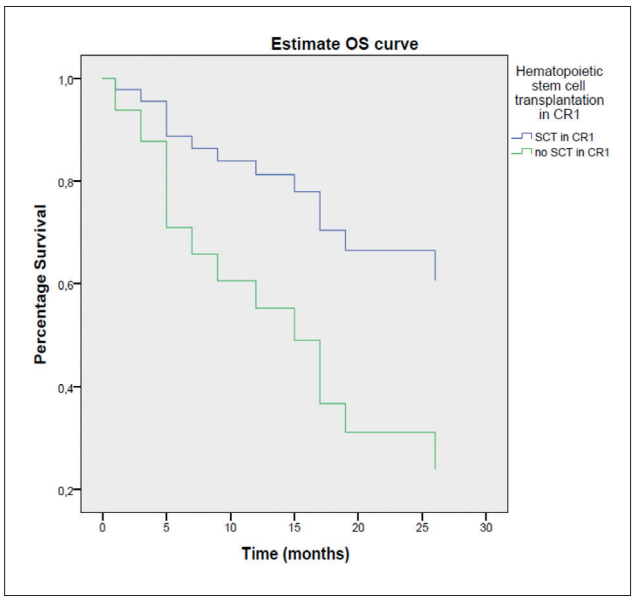

FIGURE 3. Impact of allogeneic SCT in CR1 on OS independent of age. HR 0.349, p=0.073.

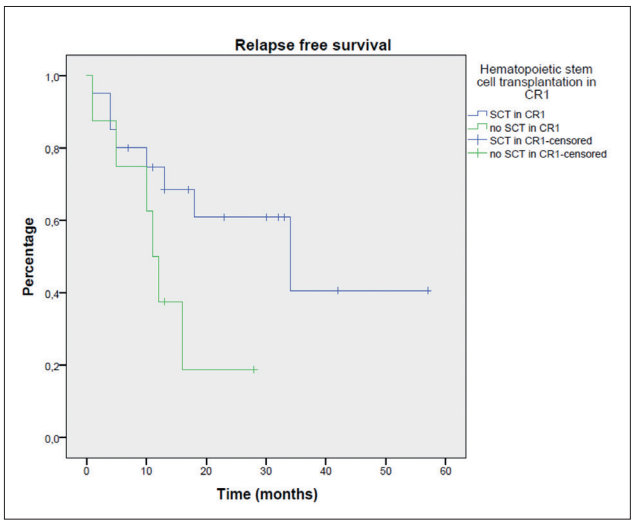

FIGURE 4. Comparison of RFS (in months) for patients receiving allogeneic SCT in CR1 (n=21) *vs.* patients not receiving allogeneic SCT on organisational grounds (n=8). HSCT in CR1: median RFS 34 months, no HSCT in CR1: median RFS 11 months, p=0.071.

point the patient was last known to be alive. Patients were administratively censored at last contact.

For univariate comparisons, the Fisher's exact test and Mann-Whitney U test were used. Survival curves were estimated using the Kaplan-Meier strategy and were compared using the log-rank test. For multivariate analysis, a cox regression analysis was performed. Patient characteristics that were associated with RFS with p-values <0.1 by univariate analysis were included in the model. To avoid overfitting, the World Health Organization (WHO) classification was omitted from the analysis. We acknowledge that we are losing information in doing so, but we assume to include part of this information in the model with use of the 'age' variable. Reported p-values are two-sided with a significance level of 0.05.

RESULTS

A total of 161 newly diagnosed AML patients were identified

TABLE 2. Multivariate cox regression analysis for relapse-free survival.

Variable	Hazard ratio (95% CI)	p
HSCT	0.388 (0.152-0.989)	0.047
Age >60	1.016 (0.983-1.049)	0.351

HSCT: haematopoietic stem cell transplantation, CI: confidence interval.

during the study period and included 43 IR patients eligible for intensive chemotherapy (cohort 1: n=17, cohort 2: n=26). Patients from cohort 1 were older (63 years *vs* 50.5 years, p=0.009), had a lower white blood cell (WBC) count at diagnosis (70.6% had ≤10,000 WBC/μL *vs* 34.6% in cohort 2, p=0.043) and, as expected, were less likely to receive an allogeneic SCT (four patients [23.5%] *vs* seventeen patients [65.4%] in cohort 2, p=0.012). There seemed to be a difference in the distribution of the different WHO categories between both cohorts (notably more patients had AML with myelodysplasia-related changes [AML-MRC] in cohort 1, which is in accordance with the age difference), but this was not statistically significant, (p=0.066) probably due to a lack of power (*Table 1*).

No statistically significant difference in RFS could be found between both cohorts. Median RFS was twelve months for patients in cohort 1 *vs*. eighteen months for patients in cohort 2 (p=0.747)(*Figure 1*).

In order to identify prognostic factors for RFS, we performed a univariate analysis comparing patients who did not experience disease relapse (n=15) with patients who either experienced disease relapse or died (n=21). This revealed several significant risk factors for relapse/death: age >60 years, not receiving allogeneic SCT in CR1 and WHO classification. Based on these results, we performed an unplanned multivariate cox-regression analysis for RFS in all IR patients receiving intensive chemotherapy during the entire study period. This showed that receiving an allogeneic SCT in CR1 significantly improved RFS (HR 0.388, 95% CI 0.152-0.989, p=0.047) with a trend towards better OS (HR 0.349, 95% CI 0.111-1.101, p=0.073) independent of age (*Figures 2, 3 & Table 2*).

In order to eliminate the effect of other confounding factors besides age (e.g., comorbidities), an additional analysis was performed comparing patients who received an allogeneic SCT (n=21) with those patients who were eligible for transplant but could not proceed to transplant on organisational grounds (patient wishes, the absence of a suitable donor; n=9). Although not reaching statistical significance, this analysis showed an improved RFS in patients who received an allogeneic SCT (median RFS of 34 months *vs* 11 months, p=0.071, *Figure 4*).

DISCUSSION

The goal of this study was to investigate the impact of newly implemented treatment guidelines pertaining to the indication for allogeneic SCT on RFS in IR AML patients. We expanded our research with an exploratory analysis showing a benefit of allogeneic SCT on the outcome in IR patients. However, a number of important elements need to be taken into account when interpreting the results.

First of all, there seems to be an important difference between cohort 1 and cohort 2, with patients in cohort 1 being significantly older and, consequently, with a much higher percentage of AML-MRC in cohort 1, although not statistically significant.

Secondly, due to the low number of patients, this study was not adequately powered to establish a statistically significant difference in RFS between cohort 1 and cohort 2, nor was it powered for the additional exploratory analyses.

Another point to be addressed is our use of the ELN 2017 criteria to identify the patients' risk profile.[3] The research into the benefit of allogeneic SCT as a consolidation treatment in IR patients was for the most part done using older classifications such as the ELN 2010 criteria.[5] Due to the integration of novel molecular markers (e.g., RUNX1 and ASXL1) in the novel ELN criteria and the widespread use of next generation sequencing used in the diagnostic process, risk stratification has known a profound change over the past years potentially impacting the influence of treatment strategies. Therefore, the impact of allogeneic SCT in our population might differ from what is expected from the literature.

Ideally, to gauge the impact of allogeneic SCT as a post-remission strategy, a prospective 'donor *vs* no donor' set-up would be preferred, but as alternative donor strategies gain importance, these trials are more difficult to perform, as most patients will have an available donor. This study at-

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Treatment of acute myeloid leukaemia patients needs to be tailored according to the underlying risk category.**
2. **Intermediate-risk patients who are fit for intensive chemotherapy most likely benefit from consolidation with allogeneic stem cell transplantation in first complete remission.**
3. **Consolidation with chemotherapy alone remains a viable treatment option in those intermediate-risk acute myeloid leukaemia patients where allogeneic stem cell transplantation cannot be performed due to exceptional circumstances (no donor available, patient choice, etc.).**

tempted to simulate this setting by comparing patients who received an allogeneic SCT with patients who did not solely on organisational grounds. However, due to the very small number of patients who did not receive an allogeneic transplantation on organisational grounds, the results must be interpreted with caution.

CONCLUSION

The primary endpoint of this study was not reached: the introduction of the new care program prescribing allogeneic SCT for IR AML patients was not associated with a significant improvement in RFS. Further research into the impact of allogeneic SCT in IR patients is warranted, especially now that risk stratification has shifted due to the inclusion of novel molecular data. Nevertheless, exploratory analysis of the entire group of IR patients treated with intensive chemotherapy suggests a survival benefit from allogeneic SCT, with significantly improved RFS and a trend towards a better OS. However, consolidation with chemotherapy alone remains a viable treatment option in those patients where allogeneic SCT cannot be performed due to the lack of a donor or patient wishes.

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