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Clinical outcomes and treatment patterns in adult patients with FMS-like tyrosine kinase 3 internal tandem duplication positive acute myeloid leukemia undergoing allogeneic hemopoietic cell transplantation in the US and Canada: Center for International Blood and Marrow Transplant Research analysis

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INTRODUCTION & OBJECTIVE

- Allogeneic hemopoietic cell transplantation (allo-HCT) is the preferred consolidation therapy for patients with AML and internal tandem duplication of the FMS-like tyrosine kinase 3 gene (*FLT3*-ITD^{mut+}), who have achieved first complete remission[1,2]
- However, the impact of key characteristics on clinical outcomes following allo-HCT are not fully understood
- The **objective of this study** was to determine the impact of patient, disease and transplant characteristics on outcomes, trends in maintenance therapy, and causes of death for patients aged ≥18 years with *FLT3*-ITD^{mut+} AML undergoing first allo-HCT

METHODS

- **Observational cohort study** of recipients of allo-HCT (human leukocyte antigen identical sibling, haploidentical, 8/8 or 7/8 unrelated, or cord blood donor) in the US and Canada between 01 Jan 2014 and 31 Dec 2019 reported in the Center for International Blood and Marrow Transplant Research database
- Patients enrolled in NCT02997202 (post-allo-HCT gilteritinib maintenance) were excluded

Outcomes evaluated:

- Main:
  - Overall survival (OS)
  - Leukemia-free survival (LFS)
- Other:
  - Relapse
  - Non-relapse mortality (NRM; death while in remission)

Statistical methods:

- Outcomes measured from the time of allo-HCT by disease status: first complete remission (CR1); second or greater CR (≥CR2); relapsed/refractory (R/R)
- Multivariable analyses conducted using Cox proportional hazards models

CONCLUSIONS

- **Timing of allo-HCT is important: more advanced disease, older age, and longer time from diagnosis or CR to HCT may be associated with poorer outcomes in patients with *FLT3*-ITD^{mut+} AML undergoing allo-HCT**
- **Future research should focus on timing of HCT and impact of maintenance therapy to prevent post-HCT AML-related deaths**

RESULTS

- A total of 3147 patients were followed for a median (range) of 43 (3–90) months at 150 centers in the United States and Canada
- Median (range) age at HCT was 55 (18–80) years, 53% (n=1679) of patients were female, and the majority (81%, n=2540) of patients were White
- Disease status at allo-HCT was: CR1, n=2389; ≥CR2, n=340; R/R, n=418
- There was an increase in the use of maintenance therapy from 2014 to 2019 (11% to 47%, respectively), **mainly associated with increased use of *FLT3* inhibitors** (8% to 40%, respectively)
- The **most common cause of death** was AML (60%), followed by infection (12%)

Overall survival

- **Advanced disease status at time of HCT, fludarabine (Flu) + melphalan (Mel) ± others conditioning regimen, higher HCT-comorbidity index (CI),** and **longer time from diagnosis to HCT** were significantly associated with shorter OS **(Figure 1)**
- OS was significantly shorter with in patients with ≥CR2 and R/R disease versus those with CR1 disease, and also in those with R/R versus ≥CR2 disease **(Figure 1)**

Leukemia-free survival

- At both ≤2.6 months and >2.6 months, **≥CR2 and R/R disease status** were significantly associated with shorter LFS, compared with CR1 **(Figure 2)**
- **Older age (≥50 years) at allo-HCT, reduced-intensity/nonmyeloablative (RIC/NMA) conditioning, Flu + Mel ± others conditioning regimen,** and **higher HCT-CI score (≥1)** were significantly associated with shorter LFS **(Figure 2)**

Relapse

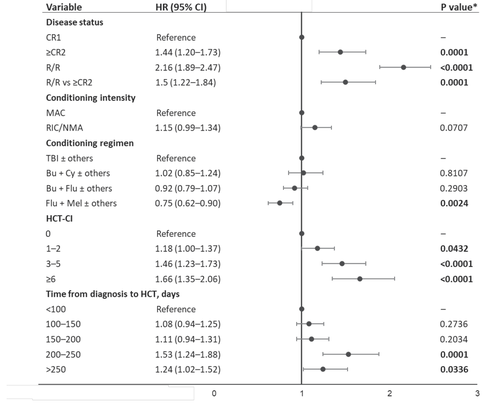
- **Advanced disease status, RIC/NMA conditioning, busulfan + Flu ± others and Flu + Mel ± others conditioning regimens, higher HCT-CI score,** and **longer time from CR to HCT** were significantly associated with increased risk of relapse **(Figure 3)**
- Risk of relapse was significantly greater for patients with **R/R than ≥CR2 disease beyond 2.6 months (Figure 3)**

Non-relapse mortality (NRM)

- While no association was found between disease status and NRM, **haploidentical, partially matched unrelated and mismatched unrelated donor types, peripheral blood stem cell graft type, higher HCT-CI score,** and **longer time from diagnosis to HCT** were associated with greater risk of NRM **(Figure 4)**

Figure 1. Characteristics associated with inferior overall survival

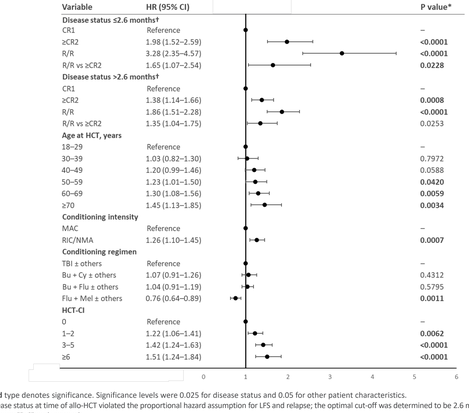
Variable	HR (95% CI)	P value*
Disease status		
CR1	Reference	–
≥CR2	1.44 (1.20–1.73)	**0.0001**
R/R	2.16 (1.89–2.47)	**<0.0001**
R/R vs ≥CR2	1.5 (1.22–1.84)	**0.0001**
Conditioning intensity		
MAC	Reference	–
RIC/NMA	1.15 (0.99–1.34)	0.0707
Conditioning regimen		
TBI ± others	Reference	–
Bu + Cy ± others	1.02 (0.85–1.24)	0.8107
Bu + Flu ± others	0.92 (0.79–1.07)	0.2903
Flu + Mel ± others	0.75 (0.62–0.90)	**0.0024**
HCT-CI		
0	Reference	–
1–2	1.18 (1.00–1.37)	**0.0432**
3–5	1.46 (1.23–1.73)	**<0.0001**
≥6	1.66 (1.35–2.06)	**<0.0001**
Time from diagnosis to HCT, days		
<100	Reference	–
100–150	1.08 (0.94–1.25)	0.2736
150–200	1.11 (0.94–1.31)	0.2034
200–250	1.53 (1.24–1.88)	**0.0001**
>250	1.24 (1.02–1.52)	**0.0336**



*Bold type denotes significance. Significance levels were 0.025 for disease status and 0.05 for other patient characteristics.
Bu, busulfan; CI, confidence interval; CMV, cytomegalovirus; CR1, first complete remission; CR2, second complete remission; Cy, cyclophosphamide; Flu, fludarabine; HCT-CI, hemopoietic cell transplantation-comorbidity index; HR, hazard ratio; HCT, hemopoietic cell transplantation; MAC, myeloablative conditioning; Mel, melphalan; NMA, nonmyeloablative conditioning; RIC, reduced-intensity conditioning; R/R, relapsed/refractory; TBI, total body irradiation
Stratified by patient age and CMV match.

Figure 2. Characteristics associated with inferior leukemia-free survival

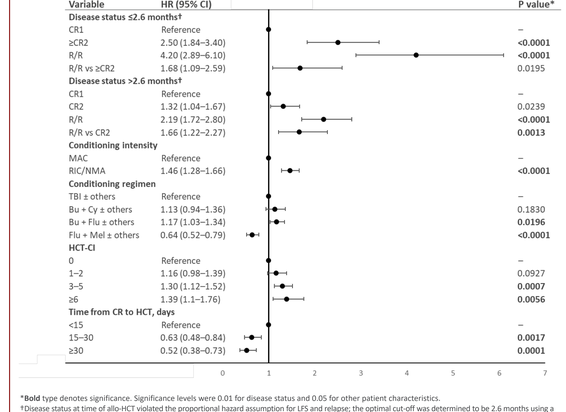
Variable	HR (95% CI)	P value*
Disease status ≤2.6 months†		
CR1	Reference	–
≥CR2	1.98 (1.52–2.59)	**<0.0001**
R/R	3.28 (2.35–4.57)	**<0.0001**
R/R vs ≥CR2	1.65 (1.07–2.54)	**0.0228**
Disease status >2.6 months†		
CR1	Reference	–
≥CR2	1.38 (1.14–1.66)	**0.0008**
R/R	1.86 (1.51–2.28)	**<0.0001**
R/R vs ≥CR2	1.35 (1.04–1.75)	0.0253
Age at HCT, years		
18–29	Reference	–
30–39	1.03 (0.82–1.30)	0.7972
40–49	1.20 (0.99–1.46)	0.0588
50–59	1.23 (1.01–1.50)	**0.0420**
60–69	1.30 (1.08–1.56)	**0.0059**
≥70	1.45 (1.13–1.85)	**0.0034**
Conditioning intensity		
MAC	Reference	–
RIC/NMA	1.26 (1.10–1.45)	**0.0007**
Conditioning regimen		
TBI ± others	Reference	–
Bu + Cy ± others	1.07 (0.91–1.26)	0.4312
Bu + Flu ± others	1.04 (0.91–1.19)	0.5795
Flu + Mel ± others	0.76 (0.64–0.89)	**0.0011**
HCT-CI		
0	Reference	–
1–2	1.22 (1.06–1.41)	**0.0062**
3–5	1.42 (1.24–1.63)	**<0.0001**
≥6	1.51 (1.24–1.84)	**<0.0001**



*Bold type denotes significance. Significance levels were 0.025 for disease status and 0.05 for other patient characteristics.
†Disease status at time of allo-HCT violated the proportional hazard assumption for LFS and relapse; the optimal cut-off was determined to be 2.6 months using a maximum likelihood approach.
Stratified by MRD-negative status and CMV match.
Bu, busulfan; CI, confidence interval; CMV, cytomegalovirus; CR1, first complete remission; CR2, second complete remission; Cy, cyclophosphamide; Flu, fludarabine; HCT-CI, hemopoietic cell transplantation-comorbidity index; HR, hazard ratio; HCT, hemopoietic cell transplantation; MAC, myeloablative conditioning; Mel, melphalan; MRD, minimal residual disease; NMA, nonmyeloablative conditioning; RIC, reduced-intensity conditioning; R/R, relapsed/refractory; TBI, total body irradiation.

Figure 3. Characteristics associated with higher relapse rate

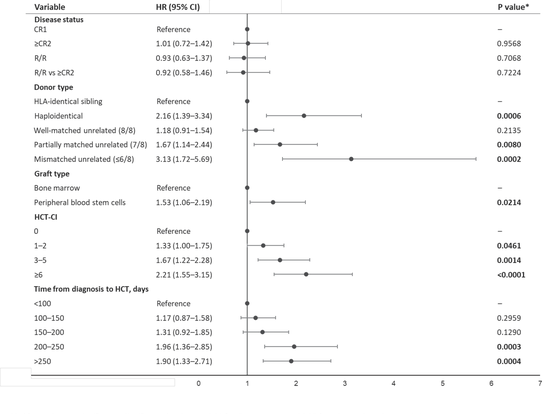
Variable	HR (95% CI)	P value*
Disease status ≤2.6 months†		
CR1	Reference	–
≥CR2	2.50 (1.84–3.40)	**<0.0001**
R/R	4.20 (2.89–6.10)	**<0.0001**
R/R vs ≥CR2	1.68 (1.09–2.59)	0.0195
Disease status >2.6 months†		
CR1	Reference	–
CR2	1.32 (1.04–1.67)	0.0239
R/R	2.19 (1.72–2.80)	**<0.0001**
R/R vs CR2	1.66 (1.22–2.27)	**0.0013**
Conditioning intensity		
MAC	Reference	–
RIC/NMA	1.46 (1.28–1.66)	**<0.0001**
Conditioning regimen		
TBI ± others	Reference	–
Bu + Cy ± others	1.13 (0.94–1.36)	0.1830
Bu + Flu ± others	1.17 (1.03–1.34)	**0.0196**
Flu + Mel ± others	0.64 (0.52–0.79)	**<0.0001**
HCT-CI		
0	Reference	–
1–2	1.16 (0.98–1.39)	0.0927
3–5	1.30 (1.12–1.52)	**0.0007**
≥6	1.39 (1.1–1.76)	**0.0056**
Time from CR to HCT, days		
<15	Reference	–
15–30	0.63 (0.48–0.84)	**0.0017**
≥30	0.52 (0.38–0.73)	**0.0001**



*Bold type denotes significance. Significance levels were 0.01 for disease status and 0.05 for other patient characteristics.
†Disease status at time of allo-HCT violated the proportional hazard assumption for LFS and relapse; the optimal cut-off was determined to be 2.6 months using a maximum likelihood approach.
Stratified by MRD-negative status.
Bu, busulfan; CI, confidence interval; CR1, first complete remission; CR2, second complete remission; Cy, cyclophosphamide; Flu, fludarabine; HCT-CI, hemopoietic cell transplantation-comorbidity index; HR, hazard ratio; HCT, hemopoietic cell transplantation; MAC, myeloablative conditioning; Mel, melphalan; MRD, minimal residual disease; NMA, nonmyeloablative conditioning; RIC, reduced-intensity conditioning; R/R, relapsed/refractory; TBI, total body irradiation.

Figure 4. Characteristics associated with higher likelihood of non-relapse mortality

Variable	HR (95% CI)	P value*
Disease status		
CR1	Reference	–
≥CR2	1.01 (0.72–1.42)	0.9568
R/R	0.93 (0.63–1.37)	0.7068
R/R vs ≥CR2	0.92 (0.58–1.46)	0.7224
Donor type		
HLA-identical sibling	Reference	–
Haploidentical	2.16 (1.39–3.34)	**0.0006**
Well-matched unrelated (8/8)	1.18 (0.91–1.54)	0.2135
Partially matched unrelated (7/8)	1.67 (1.14–2.44)	**0.0080**
Mismatched unrelated (≤6/8)	3.13 (1.72–5.69)	**0.0002**
Graft type		
Bone marrow	Reference	–
Peripheral blood stem cells	1.53 (1.06–2.19)	**0.0214**
HCT-CI		
0	Reference	–
1–2	1.33 (1.00–1.75)	**0.0461**
3–5	1.67 (1.22–2.28)	**0.0014**
≥6	2.21 (1.55–3.15)	**<0.0001**
Time from diagnosis to HCT, days		
<100	Reference	–
100–150	1.17 (0.87–1.58)	0.2959
150–200	1.31 (0.92–1.85)	0.1290
200–250	1.96 (1.36–2.85)	**0.0003**
>250	1.90 (1.33–2.71)	**0.0004**



*Bold type denotes significance. Significance levels were 0.01 for disease status and 0.05 for other patient characteristics.
Stratified by patient age, CMV match, and GVHD prophylaxis.
CI, confidence interval; CMV, cytomegalovirus; CR1, first complete remission; CR2, second complete remission; GvHD, graft-versus-host disease; HCT-CI, hemopoietic cell transplantation-comorbidity index; HLA, human leukocyte antigen; HR, hazard ratio; HCT, hemopoietic cell transplantation; R/R, relapsed/refractory.

Author disclosures
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