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FLT3

Sorafenib associated with improved outcomes for patients with FLT3-ITD AML

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Approximately 25% of patients with acute myeloid leukemia (AML) have internal tandem duplication of FMS-like tyrosine kinase 3 (FLT3-ITD) mutations and survival is often inferior due to high relapse rates and short remission periods.[1] Since the optimal therapy is challenging for patients with FLT3-ITD AML who relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT), sorafenib, as monotherapy or in combination, has recently been suggested to be an option for salvage therapy.

Li Xuan, from the Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou, CN, and colleagues retrospectively evaluated the efficacy of sorafenib combined with other therapeutic strategies for patients with FLT3-ITD AML, who had relapsed after allo-HSCT

Patient characteristics

Patients with FLT3-ITD mutations at relapse after allo-HSCT recruited from seven hospitals (Nanfang Hospital, Peking University People's Hospital, First Affiliated Hospital of Soochow University, Institute of Hematology and Blood Diseases Hospital, Xinqiao Hospital, Zhujiang Hospital and First People's Hospital of Chenzhou) were assessed retrospectively between January 2012 and October 2017.

	Entire sample, n = 83	Sorafenib, n = 53	Non-sorafenib, n = 30	*P* value
Median age at transplant, years, (range)	36 (14—59)	37 (15—59)	35 (14—57)	0.758
Gender				0.834
Male	43 (51.8%)	27 (50.9%)	16 (53.3%)	
Female	40 (48.2%)	26 (49.1%)	14 (46.7%)	
Disease status at transplant				0.677

CR	58 (69.9%)	38 (71.7%)	20 (66.7%)	
PR	7 (8.4%)	5 (9.4%)	2 (6.7%)	
NR	18 (21.7%)	10 (18.9%)	8 (26.7%)	
Donor type				0.685
HLA-matched sibling	31 (37.3%)	18 (34.0%)	13 (43.3%)	
HLA-matched unrelated	10 (12%)	7 (13.2%)	3 (10.0%)	
HLA-Haploidentical related	45 (50.6%)	28 (52.8%)	14 (46.7%)	
Sorafenib use before relapse				0.627
Use	33 (54.1%)	18 (51.4%)	15 (57.7%)	
No use	28 (45.9%)	17 (48.6%)	11 (42.3%)	
aGvHD before relapse				0.588
No aGvHD	55 (66.3%)	34 (64.2%)	21 (70.0%)	

Table 1: Patient characteristics, entire sample and sorafenib groups

	DLI group (n = 53)	Non-DLI group (n = 25)	*P* value
Median age at transplant, years, (median)	37 (14—57)	35 (17—59)	0.506

Gender			0.982
Male	30 (51.7%)	13 (52.0%)	
Female	28 (48.3%)	12 (48.0%)	
Disease status at transplant			0.091
CR	41 (70.7%)	17 (68.0%)	
PR	7 (12.1%)	0 (0.0%)	
NR	10 (17.2%)	8 (32.0%)	
Donor type			0.481
HLA-matched sibling	24 (41.1%)	7 (28.0%)	
HLA-matched unrelated	7 (12.1%)	3 (12.0%)	
HLA-Haploidentical related	27 (46.5%)	15 (60.0%)	
Sorafenib use before relapse			0.814
Use	21 (55.3%)	12 (52.2%)	
No use	17 (44.7%)	11 (47.8%)	
aGvHd before relapse			*0.001
No aGvHD	45 (77.6%)	10 (40.0%)	

Table 2: Patient characteristic, donor lymphocyte infusion (DLI) groups, on the basis of DLI inclusion in salvage therapy

Methods

- Genomic DNA was extracted from bone marrow and analyzed to confirm FLT3-ITD mutation
- At relapse, following allo-HSCT, immune suppressants were immediately stopped and salvage therapy began
- Four salvage regimens were adopted:
  - Group A: sorafenib combined with chemotherapy followed by DLI (n = 41)
  - Group B: sorafenib combined with chemotherapy (n = 12)
  - Group C: chemotherapy followed by DLI (n = 17)
  - Group D: monochemotherapy (n = 13)
- The chemotherapy regimens included aclacinomycin, cytarabine and granulocyte colony-stimulating factor (CAG; n = 41), idarubicin and cytarabine (IA, n = 25) and other (n = 17)
- Sorafenib started at 400mg twice daily and adjusted based on suspected toxicity (range, 200—800mg daily)
- A total of 78 doses was given to 58 patients (median, 1; range, 1—3 times) at a median dosage of $3.2x10^7$ (range, $1.5x10^7$—$7.1x10^7$) $CD3^+$ T cells/kg

Results

	Entire sample, n = 83	Group A	Group B	Group C	Group D	*P* value
CR	44 (53.0%)	29 (70.7%)	6 (50.0%)	6 (35.3%)	3 (23.1%)	*0.007
OR	59 (71.1%)	36 (87.8%)	8 (66.7%)	10 (58.8%)	5 (38.5%)	*0.003
1-year incidence of aGvHD after salvage therapy	32.0% (CI 22.1%—42.4%)	39.5% (CI 24.4%—54.3%)	29.4% (CI 9.4%—51.9%	34.7% (CI 10.2%—62.4%)	7.7% (CI 0.4%—30.4%	0.242
1-year incidence of cGvHD after salvage therapy	28.1% (CI 17.8%—38.3%)	32.8% (CI 18.2%—48.3)	27.1% (CI 5.6%—55.4%)	35.8% (CI 8.9%—64.6%)	0.0%	0.276
1-year mortality of GvHD after salvage therapy	3.6% (CI 1.0%—9.4%)	2.4% (CI 0.2%—11.2%)	8.3% (CI 0.3%—33.7%)	5.9% (CI 0.3%—25.1%)	0.0%	0.662

1-year OS	37.2% (CI 26.8%—47.5%)	53.2% (CI 36.9%—67.1%)	25.0% (CI 6.0%—50.5%)	23.5% (CI 7.3%—44.9%)	15.4% (CI 2.5%—38.8%)	*0.003
1-year PFS	34.7% (CI 24.7%—45.0%)	50.8% (CI 34.6%—64.9%)	25.0% (CI 6.0%—50.5%)	23.5% (CI 7.3%—44.9%)	7.7% (CI 0.5%—29.2%)	*<0.001
1-year GRFS	30.2% (CI 20.6%—40.4%)	41.8% (26.3%—56.6%)	25.0% (6.0%—50.5%)	23.5% (7.3%—44.9%)	7.7% (0.5%—29.2%)	*0.018
1-year NRM	15.7% (CI 8.8%—24.3%)	12.4% (CI 4.4%—24.7%)	25.0% (CI 5.0%—52.6%)	23.5% (CI 6.7%—46.1%)	15.4% (CI 2.1%—40.5%)	0.763

Table 3: Outcomes after salvage therapy. OS = overall survival, PFS = progression-free survival, GRFS = GvHD-free/relapse-free survival, NRM = non-relapse mortality. *P<0.05

- After a median follow-up of 251 days (range, 30—1992) after relapse:
- 29 patients were living
- 54 patients deceased, causes included
  - Leukemia progression, n = 39
  - Infection, n = 9
  - GvHD, n = 3
  - Other, n = 3

Key findings

- 1-year OS, PFS, and GRFS of the sorafenib groups were superior to those of the non-sorafenib group
  - OS: 46.8% vs 20.0%, $P = 0.003$
  - PFS: 44.9% vs 16.7%, $P = 0.001$
  - GRFS: 37.9% vs 16.7%, $P = 0.015$
- 1-year OS, PFS, and GRFS of the DLI group was also statistically superior to those of the non-DLI group ($P < 0.03$)
- Subgroups analysis:
  - OS and PFS of Group A were statistically superior to Groups B, C and D (all $P < 0.05$)
  - GRFS in Group A was statistically superior to that of Group D ($P = 0.002$)
  - No significant difference in OS, PFS, and GRFS in Groups B, C, and D

- Multivariate analysis:
  - Sorafenib was the only protective factor for longer OS (*P* = 0.035; HR 0.526)
  - Salvage therapy including sorafenib (*P* = 0.011; HR 0.423) and DLI (*P* = 0.019; HR = 0.508) were the protective factors for longer PFS

Conclusion

The study found that salvage therapy containing sorafenib was superior with regards to OS, PFS, and GRFS for patients with FLT3-ITD AML. Results showed that salvage therapy with sorafenib combined with chemotherapy followed by DLI improved OS and PFS, over chemotherapy alone, chemotherapy followed by DLI and chemotherapy combined with sorafenib. The results indicate that the induction of graft-versus-leukemia effect through allogenic immune cells can be enhanced by sorafenib.

The number of patients in the study was relatively small, and as the data was assessed retrospectively, well-designed clinical trials are necessary to establish whether sorafenib therapy, combined with chemotherapy and followed by DLI, would result in optimal outcomes for patients.

Reference

1. DeZern A.E., *et al*. Role of allogeneic transplantation for FLT3/ITD acute myeloid leukemia: outcomes from 133 consecutive newly diagnosed patients from a single institution. *Biol Blood Marrow Transplant*. 2011 Sep 1. 17(9):1404-9. DOI: 1016/j.bbmt.2011.02.003
2. Xuan L., *et al*. Sorafenib therapy is associated with improved outcomes for FLT3-ITD AML relapsing after allo-HSCT. *Biol Blood Marrow Transplant*. 2019 Apr 19. DOI: 1016/j.bbmt.2019.04.018