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Autologous hematopoietic stem cell transplantation in acute myeloid leukemia

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With the advances of allogeneic hematopoietic stem cell transplantation (allo-HSCT), the role of autologous hematopoietic stem cell transplantations (ASCT) in patients with acute myeloid leukemia (AML) have diminished.[1] However, for certain types of patients ASCT has resulted in improved clinical outcomes,[2] with relatively low relapse rates and very low non-relapse mortality (NRM). ASCT also has comparable overall survival to allo-HSCT in some patients.

Yuanqi Zhao, from the Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, CN, and colleagues, discussed the indications for ASCT therapy in patients with AML, looking at literature and clinical trials to evaluate clinical outcomes.[3]

ASCT *versus* intensive chemotherapy

- Standard chemotherapy induces morphological CR for AML, but relapse is a common cause of poor long-term survival
- Clinical outcomes were compared using 381 patients with AML in CR1[4]:
  - ASCT substantially reduced the relapse risk (RR) in all patients compared with those who did not receive ASCT
  - Seven-year leukemia free survival (LFS): 53% vs 40%, $P = 0.04$
  - For patients over 65, progression-free survival (PFS) and overall survival (OS) were significantly better in patients receiving ASCT than those not receiving the therapy
- A retrospective study[5] comparing ASCT (n = 152) and chemotherapy (n = 271) in patients with CR1 status AML found that:
  - Both 5-year OS (54% vs 40%, $P = 0.02$), and LFS (44% vs 30%, $P < 0.001$) were better in patients after ASCT compared with patients receiving chemotherapy
  - No significant difference identified in NRM

These studies suggest that ASCT is safe, with an acceptable safety profile, and is associated with low RRs and better LFS than chemotherapy alone. As data to support this came from retrospective trials, additional prospective studies would be needed to determine if this approach could lead to improve OS.

ASCT *versus* allo-HSCT

Stem cell transplantation is an important therapy for AML, and includes ASCT and allo-HSCT from both matched-sibling donors (MSDs) and matched unrelated donors (MUDs). MSD-allo-SCT is the best choice for patients with AML who are considering transplantation.[6] Despite this, ASCT can achieve comparable results to those of MSD-allo-SCT in some patients, and for intermediate-risk patients, is associated with better survival when compared with MUD-allo-SCT or mismatched sibling donor transplantation.

Study	Study type	Patient status	Treatment	OS	DFS	NRM	RR
Cornelissen *et al*[5]	Prosp	Intermediate-risk, CR1	Allo-SCT vs ASCT	60% vs 54%, *P* > 0.05			
Zittoun *et al*[7]	Prosp	CR1	MSD-allo-SCT vs ASCT vs CBT		4-year: 55% vs 48% vs 30%		
Yao *et al*[8]	Retro	CR1	ASCT vs MSD-allo-SCT	73.6% vs 74.6%, *P* = 0.616	69.1% vs 73.6%, *P* = 0.559	4.3% vs 11.2%, *P* = 0.215	26.6% vs 14.1%, *P* = 0.083
Keating *et al*[9]	Retro	CR1	MSD-allo-SCT vs ASCT	61% vs 54%, *P* = 0.19	58% vs 47%, *P* = 0.13		
Mizutani *et al*[10]	Retro	CR1	APBSCT vs MUD-BMT	66% vs 64%, *P* = 0.83	64% vs 58%, *P* = 0.16	7% vs 17%, *P* = 0.005	
Gorin *et al*[11]	Retro	CR1	ASCT vs MUD-allo-SCT	83% vs 62%, *P* = 0.008	67% vs 64%, *P* > 0.05	3.7% vs 19%, *P* < 0.000	29% vs 17%, *P* < 0.0001
Chevallier *et al*[12]	Retro	CR2	ASCT vs CBT	59% vs 50%, *P* = 0.45	57% vs 46%, *P* = 0.37		
Gorin *et al*[13]	Retro	CR1/CR2	ASCT vs haploSCT	64% vs 57%, *P* = 0.12	47% vs 48%, *P* = 0.73	4% vs 25%, *P* < 0.00001	50% vs 27%, *P* < 0.00001
Chen *et al*[14]	Retro	CR1	ASCT vs haploSCT	79.0% vs 80.1%, *P* = 0.769	66.1% vs 77.4%, *P* = 0.079		

Table 1: Comparison of ASCT *versus* allo-SCT in patients with AML. Prosp, prospective study; retro, retrospective study; DFS, disease-free survival; haploSCT, haploidentical transplantation; MUD-BMT, allogeneic bone marrow transplantation from a matched-unrelated donor; CBT, cord blood allo-SCT

Prognostic factors for ASCT in AML

Age

- In most studies, age >50 years was demonstrated to be an independent prognosis factor for poor survival in patients with AML who underwent autografting[2]
- However, in some studies age did not significantly impact outcome following ASCT in some studies[14–16]
- As age seems to be an unreliable prognostic factor, tolerance of induction treatment, cytogenetic risks and performance status should be taken into consideration

Cytogenetic and molecular risk stratification

Cytogenetic risk stratification is a crucial predictor for clinical outcomes in patients with AML after ASCT. Favourable-risk patients benefited more from ASCT compared allo-HSCT, and intermediate-risk patients showed similar outcomes to patients in the allo-SCT arm.[11] ASCT may be a feasible treatment for patients with AML who are in CR1 – predominantly for those with favourable- and intermediate-risk molecular cytogenetics.

APL

- A phase II study of arsenic trioxide (ATO) prior to ASCT in relapse APL found:[17]
- Five-year event-free survival (EFS) 65%
- Five-year OS 77%
- ASCT was efficacious and feasible for patients with relapsed APL in CR2
- OS after ASCT in patients with relapsed APL was better than in those patient who received chemotherapy and ATO[18]
- ASCT may be better than allo-SCT for patients with APL in CR2[19]
- ASCT is an effective post-remission therapy for patients with APL in CR2

AML with t(8;21) or inv(16) calligraphy

- Five-year OS in patients with AML carrying t(8;21) with isolated y chromosome following ASCT was 88.8%[20]
- ASCT was associated with a lower treatment related mortality (TRM) and a similar LFS to patients with inv(16) or t(8;21) receiving allo-SCT[21]

AML with CEBPA

- Patients with AML with double mutant CCAAT enhancer binding protein alpha (CEBPA) treated with ASCT and allo-SCT were compared with those treated with chemotherapy,[22] identifying that ASCT and allo-SCT were associated with better LFS

AML with FLT3/ITD mutation

- Both ASCT and allo-SCT were associated with lower RR, and better DFS and OS than treatment with chemotherapy alone, however, there was no difference between OS and DFS between allo-SCT and ASCT[23]

MRD status pre-ASCT

Minimal residual disease (MRD) is crucial when distinguishing whether patients with AML are eligible for ASCT, with multiparameter flow cytometry (MFC) and quantitative polymerase chain reaction (qPCR) being used to monitor MRD before and after ASCT. MRD status is seen as an independent prognostic factor for both OS and RFS after ASCT, which is a promising therapy for patients with negative MRD pre-ASCT.[24]

$CD34^+$ cell count in ASCT

Studies have shown that clinical outcomes are significantly affected by $CD34^+$ cell counts, with low $CD34^+$ cell counts negatively affecting engraftment, and higher $CD34^+$ cell counts being associated with higher RRs.[25]

Conclusions

ASCT is recommended for patients in first complete remission (CR1) with favourable and intermediate-risk AML and CR2 in patients with acute promyelocytic leukemia (APL), when a matched sibling donor is not available. Prior to ASCT, MRD status is the most important factor, and can be used to effectively predict outcomes after ASCT. Age should not be a limiting factor for conducting ASCT. Current conditioning regimens seem to favour the use of busulfan due to its high antileukemic effect and good safety profile.

Further studies are necessary to investigate the impact of molecular-targeted therapeutic drugs, along with more prospective trials on difference conditioning regimens in patients with varying molecular cytogenetics.

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